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PRESSOR PROPERTIES OF EXTRACTS FROM NORMAL AND FROM ISCHEMIC KIDNEYS

J. R. WILLIAMS JR., M.D.
NASHVILLE, TENN.

ARTHUR GROLLMAN, M.D.
BALTIMORE
AND
T. R. HARRISON, M.D.
NASHVILLE, TENN.

The problem of the possible significance of renin in the production of hypertension is fundamentally important in determining possible approaches to the therapeusis of this disorder. The available evidence on this point is, however, conflicting. Thus, Harrison, Blalock, Mason and Williams [1] and Prinzmetal, Friedman and Abramson [2] observed that extracts of ischemic dog kidneys cause a greater rise in blood pressure than do those of normal kidneys. On the other hand, Pickering and Prinzmetal [3] failed to observe an augmented pressor effect in extracts of ischemic rabbit kidneys, while Beckwith and Chanutin [4] found that the pressor activity of the kidney remnants of rats with hypertension due to subtotal nephrectomy was less than that of normal kidneys from rats with normal blood pressure.

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From the Department of Medicine, Vanderbilt University School of Medicine, and the Department of Pharmacology and Experimental Therapeutics, the Johns Hopkins University.

1. Harrison, T. R.; Blalock, A.; Mason, M., and Williams, J. R., Jr.: Relation of Kidneys to Blood Pressure: Effects of Extracts of Kidneys of Normal Dogs and of Dogs with Renal Hypertension on Blood Pressure of Rats, Arch. Int. Med. **60**:1058 (Dec.) 1937.

2. Prinzmetal, M.; Friedman, B., and Abramson, D. I.: Nature of Arterial Hypertension with Special Reference to the Role of the Kidney, Ann. Int. Med. **12**:1604, 1939.

3. Pickering, G. W., and Prinzmetal, M.: Some Observations on Renin, Pressor Substance Contained in Normal Kidney, Together with Method for Its Biological Assay, Clin. Sc. **3**:211, 1938.

4. Beckwith, J. R., and Chanutin, A.: The Pressor Effect of Kidney Extracts of Intact and Partially Nephrectomized Rats, Am. J. Physiol. **128**:562, 1940.

Several possible explanations for the divergent results obtained by previous workers suggest themselves: (1) differences in methods of preparation; (2) species differences of the animals (dog, rabbit, rat) from which the kidneys were derived, and (3) variations in the methods used in testing the extracts. The purpose of the present experiments was to test these several possibilities in an attempt to elucidate the contradictory results of previous investigators.

METHODS

Unilateral renal ischemia was produced in dogs by means of a Goldblatt clamp and in rats by partial obstruction of one renal artery with a silk ligature. After two to five days, extracts were prepared either by simple maceration of the kidneys with 2 volumes of 0.85 per cent solution of sodium chloride (saline extracts) or by grinding the kidneys into 10 volumes of 95 per cent ethyl alcohol, filtering, washing the alcohol-insoluble fraction with ether and extracting the final dried powder with a solution of sodium chloride (renin). In order to have sufficient material for repeated injections, the kidneys of 3 to 5 rats with unilateral renal ischemia were combined for each experiment.

As test objects for the pressor properties of these extracts normal rats anesthetized with pentobarbital sodium were used. The lower abdominal aorta was cannulated and connected to a small bore mercury manometer; heparin was used to prevent clotting. The extract was administered in doses calculated according to the formula:

$$\frac{(\text{Body weight in grams})^{2/3} \times 2}{100} = \text{cubic centimeters to be administered}^{5}$$

In a few of the earlier experiments the same rat was employed for alternate injections of the extracts from the normal and the ischemic kidneys. However, in most of the observations each fraction was injected into several rats and the average rise in blood pressure computed, each animal being used for only a single injection.

RESULTS

In 4 of a total of 5 comparisons, the saline extract from the ischemic kidney of a dog gave a definitely greater pressor effect than that from the normal kidney; the reverse effect was observed in the remaining instance. Likewise, the renin solution prepared by precipitation with alcohol from the macerated ischemic kidney gave a greater pressor effect than the similarly prepared extract of the normal kidney in 4 of the 5 comparisons; no difference was noted in the fifth observation. The divergent results of previous workers cannot, therefore, be accounted for by variations in the technic of preparation of the extracts.

On repeating the experiments previously outlined with rats' kidneys, we obtained results contrary to those just described. In 4 instances the extract from the normal kidney had a greater pressor effect than that from the ischemic organ. In the fifth experiment there was no appreciable difference between the two.

In 3 instances the saline extract of the rat kidneys, after being tested, was put into the ice box and further injections were made on the following day. In 2 of these 3 instances the extract of ischemic kidney, which had exerted less pressor effect when injected immediately after extraction, displayed a greater pressor effect

5. Grossman, E. B., and Williams, J. R., Jr.: Relation of Age to the Renal Pressor Substance, Arch. Int. Med. **62**:799 (Nov.) 1938.

after standing for twenty-four hours in a refrigerator. Four other observations were made in which the extracts from both the normal and the ischemic kidneys were tested by injection immediately after they were prepared and after standing for various intervals. These experiments, which are illustrated in figure 1, showed clearly that the extracts of normal kidney tend on standing to lose their pressor activity, while the similarly prepared extracts of the ischemic kidney maintain their pressor effects, or even become more active with time. However, because of the limited number of injections which could be made from the extracts of the rats' kidneys, a larger series of experiments was carried out, in which various fractions prepared from the kidneys of dogs were used.

Changes in the Pressor Property of Extracts of the Normal and Ischemic Kidneys of Dogs.—In the experiment illustrated in figure 2 *A*, saline extracts were prepared from the kidneys of a dog with unilateral renal ischemia of four days'

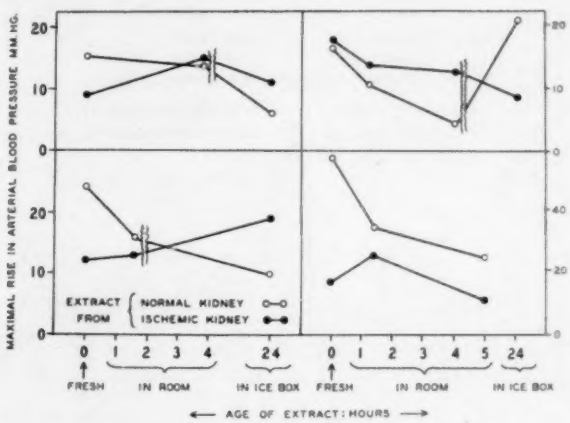

Fig. 1.—Saline extracts of the normal and the ischemic kidneys of the same rats were injected into other rats. Only the maximal pressor responses are recorded (each point represents the average maximal pressor effect in 2 rats). Although extracts from both normal and ischemic kidneys sometimes become more active and at other times less active, the general tendency was for the extracts of the normal kidney to lose pressor effect, while the extracts of the ischemic kidney tended to remain unchanged or even to become more active.

duration as rapidly as possible after their removal from the animal, under anesthesia induced with pentobarbital sodium. The extracts from each kidney were then immediately injected into each of 2 rats. The saline extracts were allowed to stand in a room at a temperature of 25 C. and the injections repeated on 4 additional rats after one hour and seven hours. The pressor effect of the extracts from the ischemic kidney was initially about twice that of extracts from the normal kidney. On standing, the extract from the ischemic kidney gradually became slightly more pressor. The saline extract of the normal kidney, on the other hand, had lost practically all of its pressor effect at the end of one hour but had considerably more pressor effect than originally at the end of seven hours.

In 2 experiments in which the pressor principle from the normal and the ischemic kidney of the same dog was precipitated with alcohol, there was a tendency for the renin solution so prepared from the normal kidney to become less active on standing, while that obtained from the ischemic kidney displayed either no significant change or some increase in its pressor activity on standing (fig. 2 *B* and *C*).

Since the renin solution made by Pickering and Prinzmetal [3] had been prepared by precipitation with 2 volumes of alcohol, while the results mentioned in this study had been obtained with fractions prepared by precipitation with 10 volumes of alcohol, the following experiment was performed: The normal and the ischemic kidney of a dog in which unilateral renal ischemia had been produced by means of a Goldblatt clamp were divided into two equal parts, one of which was ground into 1½ volumes and the other into 10 volumes of alcohol. The mixtures thus obtained were then filtered, washed with ether, dried, extracted with a solution of sodium chloride and tested on 3 rats. The kidneys were ground into the alcohol within less than one

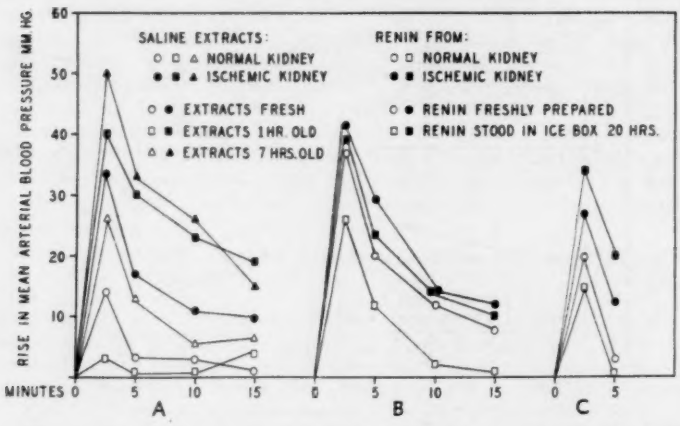

Fig. 2.—Comparison of pressor properties of the normal and the ischemic kidneys of Goldblatt dogs. The results of three different experiments are shown, each curve representing the average value on 2 to 4 rats. (*A*) Saline extract from the normal kidney of a dog with unilateral ischemia first became less active and then more active. Similar extract from the ischemic kidney showed a progressive increase in pressor effect. (*B*) On standing the renin solution from the normal kidney became less active, while that from the ischemic organ showed only a slight change. (*C*) Although the changes were slight, the renin solution from the normal kidney became less active on standing, and the reverse change occurred in the fraction from the ischemic kidney.

minute after removal from the body, and the renin solution was injected into the rats within five minutes after the solution of sodium chloride had been added to the dry powder. The various fractions were tested immediately after preparation and again after standing in the ice box for twenty-four hours. The results of this experiment are shown in figure 3. The freshly prepared extracts from this dog displayed practically no difference between the normal and the ischemic kidney, although the pressor effect of the renin prepared by precipitation with 10 volumes of alcohol was markedly greater than that made by precipitation with 1½ volumes.

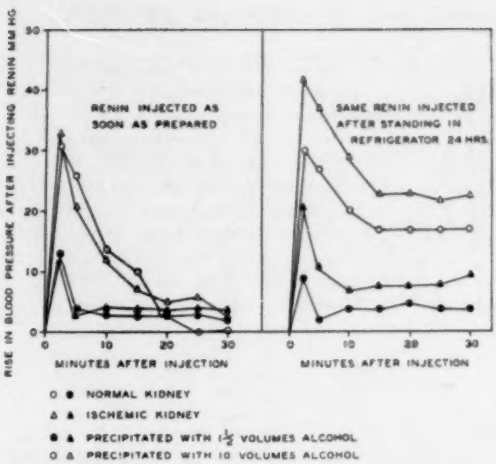
RISE IN BLOOD PRESSURE AFTER INJECTING RENIN MM HG
RENIN INJECTED AS SOON AS PREPARED
SAME RENIN INJECTED AFTER STANDING IN REFRIGERATOR 24 HRS.
MINUTES AFTER INJECTION
MINUTES AFTER INJECTION
○ ● NORMAL KIDNEY
△ ▲ ISCHEMIC KIDNEY
● ▲ PRECIPITATED WITH 1½ VOLUMES ALCOHOL
○ △ PRECIPITATED WITH 10 VOLUMES ALCOHOL

Fig. 3.—Fractions of renin freshly prepared by precipitation either with 10 or with 1½ volumes of alcohol from the normal and the ischemic kidneys were practically identical as regards pressor effect. However, after the same solutions had stood in the ice box for twenty-four hours the fractions from the ischemic kidney were decidedly more active. Each curve represents the average value for 3 rats.

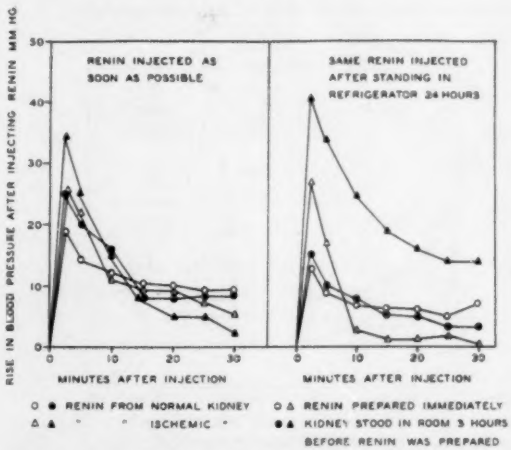
RISE IN BLOOD PRESSURE AFTER INJECTING RENIN MM HG
RENIN INJECTED AS SOON AS POSSIBLE
SAME RENIN INJECTED AFTER STANDING IN REFRIGERATOR 24 HOURS
MINUTES AFTER INJECTION
MINUTES AFTER INJECTION
○ ● RENIN FROM NORMAL KIDNEY
△ ▲ " " ISCHEMIC "
○ △ RENIN PREPARED IMMEDIATELY
● ▲ KIDNEY STOOD IN ROOM 3 HOURS BEFORE RENIN WAS PREPARED

Fig. 4.—Renin solutions prepared from portions of the normal and the ischemic kidney as soon as possible after removal from the living animal had less pressor effect than did similar solutions prepared from the remaining portions of the same kidneys which had been allowed to stand in the room for three hours. After these same renin solutions had been kept in the ice box for twenty-four hours the pressor effect of the extracts from the normal kidneys diminished, while the effect of those from the ischemic kidneys increased. In all instances the fractions from the ischemic kidney had greater activity than the similarly prepared fractions from the normal kidney of the same dog. Each curve represents the average value for 3 rats.

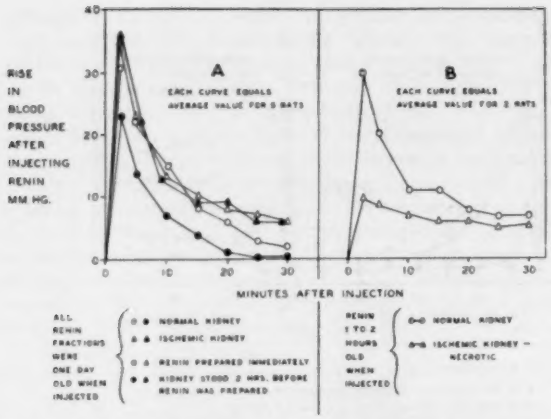
RISE IN BLOOD PRESSURE AFTER INJECTING RENIN MM HG.
A
EACH CURVE EQUALS AVERAGE VALUE FOR 5 RATS
B
EACH CURVE EQUALS AVERAGE VALUE FOR 2 RATS
MINUTES AFTER INJECTION
ALL RENIN FRACTIONS WERE ONE DAY OLD WHEN INJECTED
NORMAL KIDNEY
ISCHEMIC KIDNEY
RENIN PREPARED IMMEDIATELY
KIDNEY STOOD 2 HRS. BEFORE RENIN WAS PREPARED
RENIN 1 TO 2 HOURS OLD WHEN INJECTED
NORMAL KIDNEY
ISCHEMIC KIDNEY — NECROTIC

Fig. 5.—(*A*) One half of each kidney was ground into alcohol immediately, the other half being allowed to stand in the room for two hours before being treated with alcohol. The normal kidney lost pressor effect on standing. No significant change occurred in the ischemic kidney. (*B*) When the Goldbatt clamp was applied so snugly as to produce necrosis, the necrotic kidney had decidedly less pressor effect than did the normal organ from the same dog. This suggests that renin is not simply a degradation product of autolytic processes.

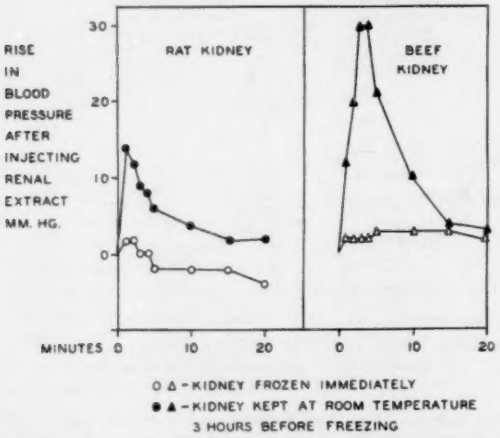
RISE IN BLOOD PRESSURE AFTER INJECTING RENAL EXTRACT MM. HG.
RAT KIDNEY
BEEF KIDNEY
MINUTES
KIDNEY FROZEN IMMEDIATELY
KIDNEY KEPT AT ROOM TEMPERATURE 3 HOURS BEFORE FREEZING

Fig. 6.—In these two experiments the extracts from kidneys frozen in liquid air as soon as they were removed from the body and subsequently dried at — 30 C. had practically no pressor effect. Similarly prepared extracts from kidneys which were allowed to stand in the room three hours before freezing had definite pressor action. (Results such as these were not regularly obtained, for in some experiments a well marked rise in blood pressure was produced by extracts of kidneys frozen immediately [fig. 7]).

After standing in the ice box overnight the pressor effects of the two fractions from the normal kidney were practically unchanged. However, the fractions from the ischemic kidney displayed a noticeably greater pressor effect than was observed on the preceding day (fig. 3).

Since both the simple saline extracts and the more purified renin solutions showed an appreciable variation in their pressor activity as the result of standing, further experiments were performed in which half of a dog's kidney was ground into alcohol immediately after removal, the other half being allowed to stand in the room for several hours before it was ground with alcohol. In the experiment illustrated in figure 4, the extract of the ischemic kidney was found to have a slightly greater pressor effect than that from the normal kidney when the fractions were injected immediately after preparation, and in both instances the extracts of the kidneys which stood in the room for three hours before being treated with alcohol had a somewhat greater pressor effect than did the fractions prepared as

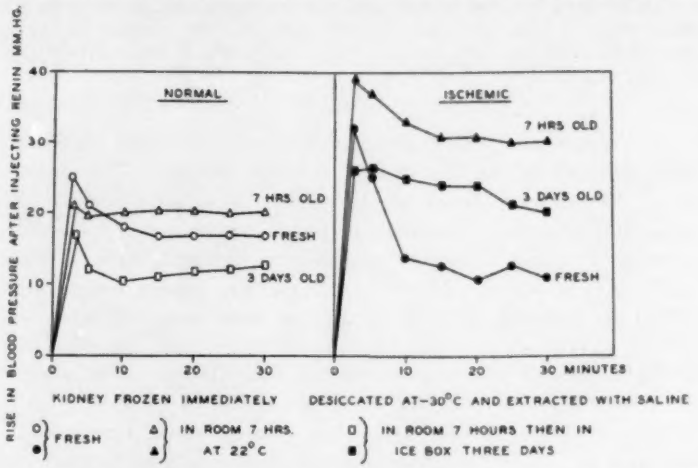

Fig. 7.—On standing seven hours the extract from the normal kidney displayed relatively little change in activity, while that from the ischemic kidney became much more active. After three days in the ice box both extracts had become less active. Each curve represents the average value for 3 rats.

soon as the kidney was removed from the body. The differences, however, were not striking with the freshly prepared fractions. On the other hand, when these same extracts, after having stood in the refrigerator for twenty-four hours, were tested again it was found that the extracts of the normal kidney had lost some of their pressor effect, while the fractions prepared from the ischemic kidney had a somewhat greater pressor effect than on the preceding day (fig. 4). In another experiment carried out similarly it was observed that the extract from the normal kidney, on standing in the room, had become less pressor, while no significant change in the pressor activity of the ischemic kidney had occurred (fig. 5 *A*).

The demonstration that the amount of renin present in a given extract often increases when the extract is allowed to stand, either in the room or in the ice box, naturally raises the question whether renin actually exists as such in the intact

kidney or whether it is an autolytic product of tissue disintegration. To determine whether autolysis in vivo causes an increase in renin content, 2 observations were made in which a Goldblatt clamp was deliberately applied so snugly to one renal artery that the vessel was almost completely occluded. Four days later the animal was killed, and the kidney was found to be necrotic. Renin solution was rapidly prepared from both the necrotic and the normal kidney by precipitation with alcohol, and in both instances the fractions from the former had much less pressor action than the similarly prepared fractions from the latter. One of these experiments is illustrated in figure 5 *B*.

In order to eliminate as much as possible autolysis in vitro, kidneys were frozen in liquid air immediately on removal from the body and dehydrated in vacuo at —30 to —70 C. The desiccated powder thus obtained was extracted with a solution of sodium chloride and immediately injected into rats. In a number of experiments extracts so prepared had practically no pressor effect, while other extracts prepared from the same kidneys at room temperature produced the usual pressor response (figure 6). On the other hand, in some instances the fractions prepared by immediate freezing and desiccation produced well marked pressor responses (fig. 7).

COMMENT

The results just presented demonstrate that the renal pressor substance designed by the term "renin" is highly unstable.[6] The degree of pressor response produced by an extract of a given kidney alters appreciably with time. Fractions prepared in such a way as to reduce enzymatic processes to an absolute minimum frequently have no demonstrable pressor action. However, such extracts usually become highly pressor on standing for a short time at room temperature or for a number of hours in the ice box. On the other hand, fractions which are highly pressor may at times become much less so on standing. It seems clear that the renin content as determined by its pressor activity is highly variable. An increase in the apparent renin content may be explained as due to the formation of pressor substance from some precursor or to the disappearance of some depressor constituent of the extract. The disappearance of renin, on the other hand, may result from its destruction or inactivation, or the pressor effect of renin may

6. In this paper the term "renin" has been used to indicate the renal pressor substance. The recent work of Kohlstaedt, Helmer and Page (Kohlstaedt, K. G.; Helmer, O. M., and Page, I. H.: Activation of Renin by Blood Colloids, Proc. Soc. Exper. Biol. & Med. **38**:214, 1938. Page, I. H.: On the Nature of the Pressor Action of Renin, J. Exper. Med. **70**:521, 1939) and of Braun-Menendez, Fasciolo, Leloir and Muñoz (Braun-Menendez, E.; Fasciolo, J. C.; Leloir, L. F., and Muñoz, J. M.: Rev. Soc. argent. de biol. **15**:420, 1939. Braun-Menendez, E., and Fasciolo, J. C.: ibid. **15**:161, 1939) shows that renin is not in fact a direct pressor substance but is an enzyme which produces a pressor substance by acting on an activator contained in the blood serum. Since, however, the same investigators have shown that there is a general parallelism between the amount of renin injected and the rise in blood pressure produced, the validity of the conclusions which were arrived at would not be affected by the mechanism of renin action.

be masked by the production of depressor substances. It is not possible at present to state with certainty the exact mechanisms responsible for the spontaneous changes in the pressor effect of renal extracts.

The processes just mentioned appear to occur in both normal and ischemic kidneys. However, the general tendency in extracts of normal kidneys is for the pressor activity to diminish. In the ischemic kidney, on the other hand, the pressor activity tends to increase.

Our experiments confirm those of Harrison, Blalock, Mason and Williams [1] and of Prinzmetal, Friedman and Abramson [2] in indicating that in the case of the dog extracts derived from the ischemic kidney usually have a more noticeable pressor effect than those from the normal kidney. Our observations on the kidneys of rats indicate that, as in the case of the rabbits studied by Pickering and Prinzmetal [3] and of the rats studied by Beckwith and Chanutin,[4] the normal kidney may have as much or more pressor activity than the abnormal kidney. However, in both the dog and the rat, extracts of the ischemic kidney tend to become more pressor on standing, while the general tendency in the case of the normal kidney is in the reverse direction, although extracts from the normal kidney may in time also become more active (figs. 1 and 2 *A* and *B*). The fundamental difference between the normal and the ischemic kidney appears to be in the rapid disappearance of the pressor activity in the normal organ and the increasing pressor activity in the ischemic organ.

The demonstration that ischemic kidneys differ from normal kidneys in their behavior as regards their renin content is compatible with the general view that renin may be concerned in the genesis of renal hypertension. Since this proposition is the subject of considerable discussion at present, it may be of interest to summarize some of the evidence for and against it.

The following observations suggest but do not prove that renin may play a role in the production of hypertension:

1. Ligation of both ureters of dogs usually causes a rise in blood pressure; removal of both kidneys does not.[7]

2. In a dog with hypertension due to ischemia of the sole remaining kidney nephrectomy is followed by a prompt decline of the blood pressure to a normal level.[8]

3. The data presented in this paper indicate that normal and ischemic kidneys may display distinct differences as to their enzymatic processes

7. Harrison, T. R.; Mason, M. F.; Resnik, H., and Rainey, J.: Changes in Blood Pressure in Relation to Experimental Renal Insufficiency, Tr. A. Am. Physicians **51**: 280, 1936.

8. Blalock, A., and Levy, S. E.: Studies on the Etiology of Renal Hypertension, Ann. Surg. **106**:826, 1937.

which produce and destroy renin. (However, it has not yet been shown that renal hypertension induced by means other than by ischemia is associated with similar changes in the kidneys, and the available evidence [4] suggests that such may not be the case.)

4. In hypertensive states there is generalized arteriolar contraction without change in the peripheral flow of blood.[9] Renin seems to be the only known pressor substance which has such an action.[10]

5. Old rats are more sensitive to renin than young animals.[5]

6. Adrenalectomy, which often reduces the blood pressure of hypertensive animals,[11] causes normal animals to become less sensitive to renin.[12]

7. Pregnancy, which in hypertensive rats causes a marked decline in blood pressure, reduces the sensitivity of normal rats to renin.[13]

8. The administration of the renal antipressor substance, which produces a decline in the blood pressure of rats with renal hypertension, causes normal rats to become less sensitive to renin.[13]

9. Some authors have reported increased vasoconstrictor effects from perfusates of ischemic kidneys as compared with those of normal kidneys.[14] (However, other workers have been unable to confirm their observations.[15])

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9. Prinzmetal, M., and Wilson, C.: The Nature of the Peripheral Resistance in Arterial Hypertension with Special Reference to the Vasomotor System, J. Clin. Investigation **15**:63, 1936.

10. Landis, E. M.; Montgomery, H., and Sparkman, D.: Effects of Pressor Drugs and of Saline Kidney Extracts on the Blood Pressure and Skin Temperature, J. Clin. Investigation **17**:189, 1938.

11. Goldblatt, H.: Studies on Experimental Hypertension: Pathogenesis of Experimental Hypertension Due to Renal Ischemia, Ann. Int. Med. **11**:69, 1937. Blalock, A., and Levy, S. E.: Studies on the Etiology of Renal Hypertension, Ann. Surg. **106**:826, 1937. Page, I. H.: Effect of Bilateral Adrenalectomy on Arterial Blood Pressure of Dogs with Experimental Hypertension, Am. J. Physiol. **122**: 352, 1938. Collins, D. A., and Wood, E. H.: Experimental Renal Hypertension and Adrenalectomy, ibid. **123**:224, 1938.

12. (*a*) Williams, J. R., Jr.; Diaz, J. T.; Burch, J. C., and Harrison, T. R.: Relation of Adrenal Glands to Action of Renal Pressor Substance, Am. J. M. Sc. **198**:212, 1939. (*b*) Friedman, B.; Somkin, E., and Oppenheimer, E. T.: The Relation of Renin to the Adrenal Gland, Am. J. Physiol. **128**:481, 1940.

13. Harrison, T. R.; Grollman, A., and Williams, J. R., Jr.: The Antipressor Action of Renal Extracts and Their Capacity to Reduce the Blood Pressure of Hypertensive Rats, Am. J. Physiol. **128**:716, 1940.

14. Fasciolo, J. C.; Houssay, B. A., and Taquini, A. C.: The Blood-Pressure Raising Secretion of the Ischemic Kidney, J. Physiol. **94**:281, 1938.

15. Mason, M. F., and Rozzell, J. D.: Attempts to Demonstrate Vasopressor Properties in the Serum of Hypertensive Dogs, Proc. Soc. Exper. Biol. & Med. **42**:142, 1939.

10. The blood of animals with experimentally produced renal hypertension contains an increased amount of renin activator.[16]

11. The amount of renin in the blood of the renal vein, as estimated by studying the vasoconstrictor effect of blood to which a given amount of renin activator has been added, is increased in hypertensive animals.

12. The hypertensive animal, like the nephrectomized animal, displays appreciable increase in sensitivity to renin.[17]

The following evidence opposes the view that renin is concerned in the genesis of hypertension:

1. It is difficult to understand how persistent hypertension can be induced by a substance which, when injected, repeatedly tends to lose its pressor effect.

2. In acute experiments destruction of the spinal cords of rats [18] and of rabbits [19] with renal hypertension causes the blood pressure to decline to a level equal to that reached by normal animals after the same procedure, but renin still exerts a pressor effect in such animals. However, in more chronic experiments chordotomy does not abolish renal hypertension.[20]

3. Extracts from either normal or ischemic kidneys prepared in such a way as to minimize enzymatic and autolytic processes have, in certain instances, exhibited practically no pressor effect.

The evidence which has been cited in favor of the significance of renin is for the most part suggestive but not conclusive. Thus, the fact that hypertension usually occurs in middle-aged or elderly persons may not be in any way related to the increased sensitivity of senile rats to renin. Some authors have found [12a] that adrenalectomy does not lower the blood pressure of hypertensive animals until the general condition deteriorates seriously, and if so the decreased sensitivity of

16. (*a*) Kohlstaedt, K. G.; Helmer, O. M., and Page, I. H.: Am. Heart J., to be published. (*b*) Page, I. H., and Helmer, O. M.: Personal communication to the authors. (*c*) Page, I. H.: Personal communication to the authors. (*d*) Braun-Menendez, E.; Fasciolo, J. C.; Leloir, L. F., and Muñoz, J. M.: La substancia hypertensora de la sangre del riñón isquemiado, Rev. Soc. argent. de biol. **15**:420, 1939.

17. (*a*) Braun-Menendez, E., and Fasciolo, J. C.: Acción vasoconstrictora e hypertensora de la sangre venosa del riñón en isquemea incompleta aguda, Rev. Soc. argent. de biol. **15**:161, 1939. (*b*) Kohlstaedt, Helmer and Page.[16a] Page.[16c]

18. Dock, W., and Rytand, D. A.: Absence of Vasoconstrictor Substance in Blood of Rats with Renal Hypertension, Proc. Soc. Exper. Biol. & Med. **32**: 374, 1934

19. Dock, W.: Personal communication to the authors.

20. Glenn, F.; Child, C. G., and Page, I. H.: The Effect of Destruction of the Spinal Cord on Hypertension Artificially Produced in Dogs, Am. J. Physiol. **122**:506, 1938.

adrenalectomized animals to renin loses its significance. Finally, the renal antipressor substance inhibits not only the effects of renin but those of certain other pressor substances as well.[18]

In view of the conflicting nature of the work bearing on the subject, final conclusions concerning the role of renin in the genesis of renal hypertension cannot be justifiably drawn at present. The available evidence suggests that some pressor substance elaborated by the kidney may be concerned in the production of hypertension, but this has not yet been proved beyond cavil.

SUMMARY

Unilateral renal ischemia was produced in dogs and in rats. Fractions were prepared from such kidneys either by extraction with a solution of sodium chloride or by precipitation with alcohol, and their pressor action determined, with the following results:

1. The extracts from the ischemic kidney of a dog usually had a distinctly greater pressor effect than the similar extracts from the normal kidney of the same animal. When the degree of ischemia was so severe as to induce necrosis the abnormal kidney had less pressor effect than the normal organ.

2. The extracts from the normal kidney of a rat had as much or more pressor effect when compared with those of the ischemic kidney of the same animal, provided the fractions were tested soon after their preparation.

3. Kidneys from both rats and dogs displayed one important similarity: On standing the extracts from the normal kidney usually became less pressor and those from the ischemic organ tended to become more pressor.

4. When enzymatic processes were reduced to a minimum by rapid freezing and desiccation of the kidneys while frozen, the extracts in many instances had practically no pressor effect. However, such inactive, freshly prepared extracts if allowed to stand usually developed a well marked pressor action.

The divergent results obtained by previous investigators in regard to the relative pressor activity of normal and ischemic kidneys were apparently due to (*a*) difference in the species of animals used as a source of kidneys and (*b*) changes occurring in the activity of the extracts after preparation.

The apparent renin content of an extract (as measured by its pressor action) is extremely variable. It may increase or decrease with time and may even be absent under certain conditions.

Dr. Irvine Page allowed us to refer to some of his work which is still unpublished.

PRIMARY BACILLUS FRIEDLÄNDER (KLEBSIELLA PNEUMONIAE) PNEUMONIA

THERAPY OF B. FRIEDLÄNDER B PNEUMONIA

ELY PERLMAN, M.D.*

AND

JESSE G. M. BULLOWA, M.D.

Clinical Professor of Medicine, New York University College of Medicine; Visiting Physician, Harlem Hospital

NEW YORK

In 1882 Friedländer [1] described a gram-negative, encapsulated bacillus which was at first regarded as the cause of pneumonia. Four years later Weichselbaum [2] demonstrated that Diplococcus pneumoniae was the more frequent etiologic agent. Recent extensive studies show that Bacillus Friedländer causes about 0.5 to 4.0 per cent of all the pneumonias and accordingly will be encountered several times a year in any large medical service.

In 1925 Avery, Heidelberger and Goebel [3] demonstrated the chemical and immunologic relationship of certain strains of this bacillus to Pneumococcus type II. The following year Julianelle [4] classified a number of strains of B. Friedländer by immunologic methods under types A, B and C with a heterologous group X. There are now available the Friedländer bacillus A and the Friedländer bacillus B serum for identification of strains by the Neufeld technic, but the B strain also swells with the

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1. Friedländer, C.: Ueber die Schizomyceten bei der acuten fibrosen Pneumonie, Virchows Arch. f. path. Anat. **87**:319, 1882.

2. Weichselbaum, A.: Ueber die Aetiologie der acuten Lungen- und Rippenfellentzündungen, Med. Jahrb. **1**:483, 1886.

3. Avery, O. T.; Heidelberger, M., and Goebel, W. F.: The Soluble Specific Substance of Friedländer's Bacillus: II. Chemical and Immunological Relationships of Pneumococcus Type II and of a Strain of Friedländer's Bacillus, J. Exper. Med. **42**:709 (Nov.) 1925.

4. Julianelle, L. A.: A Biological Classification of Encapsulatus Pneumoniae (Friedländer's Bacillus), J. Exper. Med. **44**:113 (July) 1926.

type II pneumococcus typing serum. It is important to determine the strain routinely, because only then can a better understanding of the disease, its management, its prognosis and its specific therapy be developed.

It was shown by Avery, Heidelberger and Goebel [3] that type II antipneumococcus horse serum was able to protect mice against what is now known as the B strain of B. Friedländer. Because no specific serum was available to us at the time of this study, we felt that type II antipneumococcus serum should be tried in the therapy of pneumonia due to B. Friedländer B, especially in view of the high mortality. In the case reported in this paper there were chosen from available type II antipneumococcus serums (horse and rabbit) those which, in highest dilution, produced capsule swelling when the patient's own strain of B. Friedländer B was used. The unitage of these serums in terms of their activity against B. Friedländer B [5] was estimated by Miss Frances L. Clapp, of Lederle Laboratories, Inc. The unitage is reported with the case history.

REPORT OF A CASE

W. S., a 33 year old Negro, was admitted on June 9, 1939 with a history of pleuritic pain in the right lower portion of the chest and chills beginning at 9 a. m. of the previous day. The chills were soon followed by a severe cough productive of a moderate amount of tenacious, mucopurulent, blood-streaked sputum. The patient vomited several times in the afternoon of that day and became dyspneic. Physical examination revealed a well developed man who was acutely ill, dyspneic and restless. There were marked dilatation of the alae nasi, congestion of the throat and slight edema of the eyelids. The heart was normal. Examination of the lungs showed dulness over the midportion of the right side of the chest posteriorly, with occasional crepitant rales and a friction rub at the angle of the right scapula. The abdomen was normal. The diagnosis was lobar pneumonia involving the upper and middle lobes of the right lung. The temperature was 103.2 F. and the pulse rate 124 per minute. The blood count was 3,950,000 red cells, with a hemoglobin concentration of 65 per cent (Sahli). The white cell count was 17,500, with 73 per cent polymorphonuclear leukocytes and 24 per cent lymphocytes. Chemical analysis of the blood showed: creatinine 1.4 mg., urea 15 mg., sugar 130 mg. and chlorides 410 mg. per hundred cubic centimeters. The Kahn reaction of the blood was 4 plus.

On admission to the hospital the patient was too sick for a roentgen examination. The first roentgenogram was taken on June 13 and was reported by Dr. William Snow as follows: "The chest shows consolidation of the upper lobe of the right lung, with scattered patches in the base of the right lung and the mid-

5. In a recent paper, Beeson and Goebel (J. Immunol. **38**:231 [March] 1940) stated that type II antipneumococcus rabbit serum gave none of the protection or other immunologic cross reactions against B. Friedländer B which type II horse serum gave. Experiments done in this laboratory indicate that the difference between horse and rabbit serum in this regard is one of degree. In a comparison of horse and rabbit serums of equal type II mouse-protection unitage, the horse serum is found to be approximately fifteen to thirty times as active against B. Friedländer B as rabbit serum.

portion of the left lung." The sputum showed B. Friedländer B, and the organism grew in cultures of blood taken at 10:30 a. m. and at 12 noon of the first day of hospitalization. The patient was extremely ill and coughed up large amounts of sputum typical of that seen in cases of pneumonia due to B. Friedländer, i. e., of extremely tenacious and markedly and diffusely bloody character. The cough became progressively worse and more productive, the patient bringing up 1 to 2 ounces (30 to 60 cc.) of material about every five minutes. The patient was regarded as having the acute fulminating type of Friedländer pneumonia.

Treatment was begun three hours after admission. Five grams of sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine) was given as the initial dose, followed by 1 Gm. every four hours day and night. Serum therapy was begun at the same time; over a period of twenty-four hours the patient was given a total of 594,000 units of type II antipneumococcus horse and rabbit serums. The estimated unitage of these serums indicated that the patient actually received about 25,000 units in terms of the Friedländer B bacillus.

A sample of blood taken on June 12 showed no free capsular polysaccharide when a type II antipneumococcus rabbit serum was used. A 1:2 dilution of the patient's serum in physiologic solution of sodium chloride gave a 3 plus agglutination reaction [6] with a type II suspension and a 3 plus precipitation reaction [6] with a solution of type II capsular polysaccharide. The study was done by the method described by Bukantz, Bullowa and de Gara.[7]

Course.—During the first two days the patient's course was rapidly downhill. By morning of the third day, though the temperature remained elevated, the patient began to show clinical signs of improvement. The administration of sulfapyridine was continued, and because of the delay of defervescence, on the afternoon of June 13 (the fifth day of hospitalization) 50 cc. of a 10 per cent solution of sulfapyridine in 50 per cent dextrose [8] was administered intravenously, followed in twenty-four hours by 5 Gm. of sulfapyridine sodium dissolved in 50 cc. of physiologic solution of sodium chloride, given in the same manner. The temperature dropped to 100 F. and continued to hover between 100 and 101 F. The diagnosis of pleural effusion in the right side of the chest was made and confirmed by a thoracic tap, performed on June 18, which yielded 25 cc. of a clear, yellow, sterile fluid. A roentgenogram showed two separate collections of fluid, and the patient's chest was again tapped on June 20. Six hundred cubic centimeters of fluid was removed, which was sterile. Two successive thoracic taps yielded progressively thicker fluids, which remained sterile.

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6. A 3 plus reaction is one in which a definite "button" appears but can be slightly broken up by vigorous agitation.

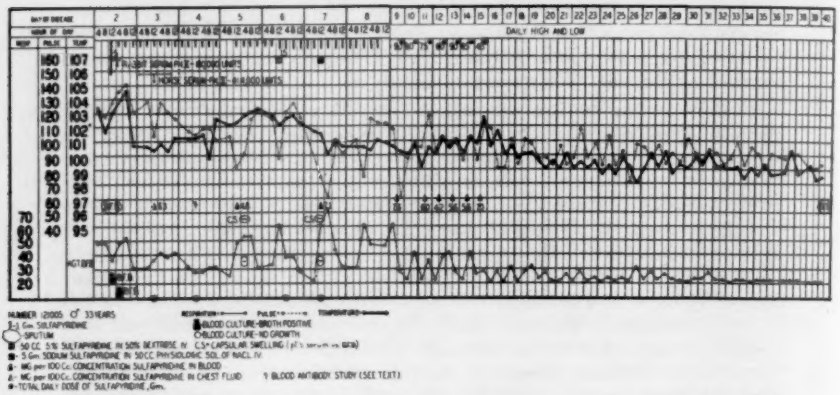
7. (*a*) Bukantz, S. C.; Bullowa, J. G. M., and de Gara, P. F.: Detection of Free Polysaccharide in Blood of Pneumococcic Pneumonia Patients: Prognosis and Therapy, Proc. Soc. Exper. Biol. & Med. **41**:250 (May) 1939. (*b*) The studies of Dochez and Avery (Soluble Substance of Pneumococcus Origin in the Blood and Urine During Lobar Pneumonia, ibid. **14**:126 [March] 1917) demonstrated that the employment of specific precipitation tests with immune serums on patients with pneumococcic pneumonia was a procedure of diagnostic as well as prognostic significance. Blake (Antigen-Antibody Balance in Lobar Pneumonia, Arch. Int. Med. **21**:779 [June] 1918) first demonstrated the presence of a positive precipitin reaction in the urine of a patient with pneumonia due to the Friedländer bacillus when the urine was tested with specific antiserum.

8. A special preparation supplied by Lederle Laboratories, Inc.

The temperature slowly returned to normal, and the patient's condition improved noticeably; he felt entirely well before the complete subsidence of the fever. By July 11 he was out of bed, and he was discharged on July 17. A culture of material taken from the throat on the day of discharge was positive for B. Friedländer B. The course and treatment are summarized in the chart.

PRESENT SERIES

Sulfapyridine was used because it was hoped that it would be as effective in the treatment of Friedländer pneumonia as it had proved itself to be in the management of the pneumococcic pneumonias. The experimental evidence in the literature, however, is contrary to this expectation. Buttle, Parish, McLeod and Stephenson [9] showed that sulfanilamide was slightly, if at all, effective in treating mice infected with the Friedländer bacillus (strain undetermined). Bliss, Feinstone, Garrett



Course of illness in a 33 year old man with pneumonia due to Bacillus Friedländer B.

and Long,[10] using the B strain, showed that sulfapyridine was slightly more effective than sulfanilamide in prolonging the survival period of the infected mice. Kolmer and Rule [11] found that in mice a slightly

9. Buttle, G. A. H.; Parish, H. J.; McLeod, M., and Stephenson, D.: The Chemotherapy of Typhoid and Some Other Non-Streptococcal Infections in Mice, Lancet **1**:681 (March 20) 1937.

10. Bliss, E. A.; Feinstone, W. H.; Garrett, A. W., and Long, P. H.: Sulfapyridine and Sulfanilamide in Experimental Pneumococcal, Meningococcal, Welch Bacillary and Friedländer's Bacillary Infections in Mice, Proc. Soc. Exper. Biol. & Med. **40**:619 (April) 1939.

11. Kolmer, J. A., and Rule, A. M.: Sulfanilamide and Sulfapyridine in the Treatment of Experimental B. Friedländer (Klebsiella Pneumoniae) Infections of Mice, Proc. Soc. Exper. Biol. & Med. **42**:305 (Oct.) 1939.

greater protection against Friedländer infections was induced by sulfapyridine than by sulfanilamide, as indicated by a longer period of survival and an occasional recovery. Sulfapyridine apparently cured a patient with "repeated B. Friedländer sepsis," type undetermined, secondary to bronchitis (Meyer and Amtman [12]). In view of these findings and the apparently successful use of sulfapyridine in the case we have reported in detail, a review was made of all the proved cases of Friedländer pneumonia recorded at Harlem Hospital since the report of Bullowa, Chess and Friedman,[13] which included the cases from July 1, 1929 through June 30, 1936. The present study includes cases from July 1, 1936 through Dec. 31, 1939. The clinical classification used is the same as that in the first report.

The criteria used for the diagnosis of Friedländer pneumonia are indicated in table 1 for each case. All doubtful cases were excluded. The difficulty of deciding whether the organisms found in the sputum are carried or are pathogenic is no greater for the Friedländer than for the pneumococcic pneumonias. The carrier incidence of an organism is no criterion of its pathogenicity. The reported carrier incidence of the Friedländer bacillus varies from 5.8 [14] to 25 per cent. In a large group of patients with miscellaneous infections of the upper respiratory tract studied in our service, the carrier incidence of the Friedländer bacillus was 2.2 per cent, as compared with a carrier incidence for pneumococci of 69 per cent.[13] With the exception of a few cases, the criteria for the diagnosis of Friedländer pneumonia as set forth by Baehr, Shwartzman and Greenspan [15] were satisfied, and, as far as possible, sources of infection other than the lung were excluded. We considered a patient to be suffering from Friedländer pneumonia when there were significant combinations of the following findings: definite clinical and roentgenologic evidence of pulmonary consolidation; repeated presence of the Friedländer bacillus and absence of other etiologic organisms in the sputum; positive blood cultures; identification of the organism in antemortem or postmortem aspirates from the lung, and presence of specific capsular polysaccharide in the blood or in the urine or in both. When both a Friedländer bacillus and a pneumococcus were found in the same case, the case was excluded, unless, as in case 18 (table 1), there was conclusive evidence that the bacillus was the causative organism.

12. Meyer, K. A., and Amtman, L.: Treatment of Friedländer's Septicemia by Sulfapyridine, with Recovery, J. A. M. A. **113**:1641 (Oct. 28) 1939.

13. Bullowa, J. G. M.; Chess, J., and Friedman, N. B.: Pneumonia Due to Bacillus Friedländeri, Arch. Int. Med. **60**:735 (Nov.) 1937.

14. Bloomfield, A. L.: The Mechanism of the Bacillus Carrier, with Special Reference to the Friedländer Bacillus, Am. Rev. Tuberc. **4**:847 (Jan.) 1921.

15. Baehr, G.; Shwartzman, G., and Greenspan, E. B.: Bacillus Friedländer Infections, Ann. Int. Med. **10**:1788 (June) 1937.

TABLE 1.—*Data Concerning Thirty-Seven Patients with Friedländer Pneumonia*

Case Number	Initials	Race	Date of Admission	Sex	Age, Years	Lobes Involved *	Sputum Typing †	Blood Culture	Clinical Classification of the Pneumonia Therapy ‡		Day of Disease on Which Therapy Was Given	Day of Disease on Which Death Occurred	Elapsed Time Between Treatment and Death	Comment
									Friedländer A Pneumonia					
1	H. H.	N	Feb. 1937	M	36	R.L.L.	+M.P.	—	Acute fulminating	307,500 units B.F. A horse serum	3d	3d	8 hr.	Postmortem cultures of lung puncture fluid and heart blood positive for B.F. A
2	A. J.	N	June 1937	F	23	R.U.L.	+M.B.	—	Subacute	None	..	Lived	.....	Spontaneous recovery with crisis on 11th day
3	C. L.	N	Dec. 1936	M	35	L.L.L.	+Sp.	—	Acute fulminating	217,500 units B.F. A horse serum	2d	3d	24 hr.	Antemortem cultures of lung puncture fluid negative; postmortem cultures of lung puncture fluid and heart blood positive for B.F. A
4	J. M.	N	Aug. 1936	M	43	R.L.L. L.U.L.	+M.P.	+	Acute fulminating	84,000 units B.F. A horse serum	2d	2d	7 hr.	Antemortem culture of lung puncture fluid positive for B.F. A
5	C. N.	N	June 1937	M	33	R.M.L. R.L.L.	+M.B.	+	Acute	720,000 units B.F. A horse serum	6th	8th	24 hr.	Blood culture on June 25 positive; blood culture on June 26 negative; temporary response to therapy ?
6	J. S.	N	Feb. 1937	M	51	R.L.L.	+Sp.	—	Acute fulminating	58,500 units B.F. A horse serum	3d	3d	3 hr.	Postmortem culture of lung puncture fluid and heart blood negative
7	C. W.	N	May 1937	M	66	R.U.L. R.M.L. R.L.L.	—	—	Acute	453,000 units B.F. A horse serum	5th	6th	26 hr.	Antemortem culture of lung puncture fluid positive for B.F. A
8	J. T.	N	Dec. 1936	M	60	R.U.L. R.L.L.	—	+	Acute	None	..	10th	.....	Postmortem cultures of pericardial fluid positive for B.F. A
9	R. R.	N	Jan. 1938	M	30	R.U.L.	—	—	Acute	None	..	9th (?)	.....	Death 2 hr. after admission; postmortem culture of heart blood positive for B.F. A
10	R. A.	N	March 1938	M	56	R.U.L. L.L.L.	+Sp.	—	Acute fulminating	540,000 units B.F. A horse serum	2d	3d	25 hr.	Postmortem culture of lung puncture fluid and heart blood positive for B.F. A
11	J. B.	N	Jan. 1938	M	43	R.U.L. R.L.L.	+M.P.	—	Acute fulminating	35,000 units B.F. A horse serum	4th	4th	1 hr.	Postmortem culture of lung puncture fluid positive for B.F. A
12	S. B.	W	Aug. 1937	M	40	L.L.L.	+Sp.	+	Acute	285,000 units B.F. A horse serum	12th	12th	4 hr.	Postmortem culture of lung puncture fluid and heart blood positive for B.F. A
13	T. Q.	W	Aug. 1937	M	41	R.L.L.	+Sp.	—	Acute	643,000 units B.F. A horse serum	4th to 10th	12th	2 days	Antemortem culture of lung puncture and thoracic tap fluid positive for B.F. A
14	D. C.	N	Oct. 1938	M	52	R.U.L. R.M.L.	+Sp.	—	Acute	Unknown unitage, B.F. A rabbit serum	3d	5th	2 days	Postmortem culture of lung puncture fluid positive for B.F. A
15	J. M.	N	April 1939	M	35	L.L.L.	+Sp.	—	Acute fulminating	5 Gm. Sp.	2d	2d	1 hr.	
16	W. J.	N	April 1939	M	73	R.L.L.	+M.P.	—	Acute	11 Gm. Sp.	?	?	4 hr.	Cardiac disease with terminal pneumonia
17	J. B.	N	March 1939	M	59	R.U.L.	+Sp.	—	Chronic	None	..	?	.....	First admission 9 mo. previously with B.F. A pneumonia; recovered with no treatment; death in March 1939; postmortem culture of lung fluid positive for B.F. A
18	R. M.	N	Aug. 1938	M	40	R.U.L.	+Sp.	+	Acute fulminating	14 Gm. S., type XIV serum	5th	Lived	.....	Type XIV pneumococcus and B.F A found on direct sputum typing; antemortem culture of lung puncture fluid positive for B.F. A only; S.S.S.§ for both B.F. A and type XIV pneumococcus found in urine
19	H. S.	N	March 1939	M	52	R.M.L. R.L.L.	+Sp.	+	Acute fulminating	1 dose B.F. A rabbit serum	4th	4th	10 min.	Patient in terminal stage on admission

19	B. S.	N	March 1939	M	52	R.M.L. R.L.L.	+Sp.	+	Acute fulminating	Probable B.F. A rabbit serum	...	...	15 min.	Patient in terminal stage on admission
20	P. C.	W	April 1939	M	63	R.L.L. R.M.L.	+Sp.	+	Acute fulminating	6 Gm. Sp.	2d	2d	3 hr.	Patient with chronic alcoholism in terminal stage on admission
21	J. B.	N	March 1939	M	61	R.L.L.	+Sp.	—	Acute fulminating	2 doses B.F. A rabbit serum	?	?	3 hr.	Postoperative pneumonia; intestinal obstruction
22	E. F.	N	Aug. 1939	M	66	R.U.L. R.L.L.	+Sp.	—	Acute fulminating	65 Gm. Sp.; 60 cc. B.F. A rabbit serum	2d	6th	4 days	Temporary response to therapy (?)
23	J. W.	N	Feb. 1939	M	40	L.U.L.	+M.P.	—	Acute fulminating	11 Gm. Sp.; 64 cc. B.F. A rabbit serum	2d	2d	1 hr. 30 min.	
24	G. V.	N	Sept. 1939	M	52	R.L.L.	+Sp.	—	Acute fulminating	None	5th	5th	.....	Death too soon after admission to permit institution of therapy
25	I. R.	N	Oct. 1939	M	42	R.L.L.	+Sp.	—	Acute fulminating	3.5 Gm. Na Sp. i.v.; 9 Gm. Sp.	1st	1st	3 hr.	Postmortem culture of heart blood positive for B.F. A
26	T. D.	N	Nov. 1939	M	37	L.L.L	+Sp.	—	Acute fulminating	84 Gm. Sp.; 10 Gm. Na Sp. i.v.	1st	Lived	.....	Development of empyema; culture of chest fluid positive for B.F. A; disappearance of B.F. A S.S.S. in chest fluid after appearance of antibodies in patient's blood
27	A. L.	N	Nov. 1939	M	43	R.U.L.	+Sp.	—	Acute	None	..	7th (?)	.....	Postmortem culture of lung puncture fluid positive for B.F. A
28	C. J.	N	Dec. 1939	M	78	L.L.L.	+M.P.	—	Acute fulminating	7 Gm. Sp.	?	?	9 hr.	Pneumonia following a prolonged drinking bout
29	M. T.	N	Nov. 1939	M	40	R.L.L.	+Sp.	—	Subacute to chronic?	27 Gm. Sp.	4th	Lived	.....	Temperature dropped to below 100 F. seven days after institution of therapy
										Friedländer B Pneumonia				
1	C. J.	N	June 1939	M	49	R.L.L.	+Sp.	+	Acute fulminating	600,000 units type II horse serum; 28 Gm. Sp.	3d to 5th	6th	30 hr.	Sp. (10 Gm.) given intravenously
2	C. P.	N	Dec. 1937	F	27	R.U.L. R.M.L. R.L.L.	+M.P.	+	Acute	None	..	Lived	.....	Antemortem culture of lung puncture fluid positive for B.F. B; spontaneous crisis on 11th day
3	M. M.	N	Sept. 1938	F	32	R.L.L. L.L.L.	+Sp.	+	Acute fulminating	5 Gm. Sp.	2d	3d	32 hr.	
4	S. B.	N	July 1939	M	51	R.L.L.	+Sp.	+	Acute	187,000 units type II rabbit serum; 44 Gm. Sp.	4th	10th	6 days	Post-traumatic pneumonia; postmortem culture of peritoneal fluid positive for B.F. B
5	R. S.	W	Oct. 1939	F	52	L.L.L.	+Sp.	—	Acute fulminating	80 cc. B.F. B rabbit serum; 16 Gm. Sp.; 10 Gm. Na Sp. i.v.	1st	2d	20 hr.	
6	G. B.	N	Oct. 1939	M	54	R.U.L. R.M.L. R.L.L.	+Sp.	—	Acute fulminating	100 cc. B.F. B rabbit serum; 18 Gm. Sp.; 10 Gm. Na Sp. i.v.	1st	3d	2 days	
7	W. S.	N	June 1939	M	33	R.U.L. R.M.L. R.L.L.	+Sp.	+	Acute fulminating	.....	..	Lived	.....	See case report in text
8	M. D.	N	Dec. 1939	F	22	L.L.L.	+M.B.	—	Acute fulminating	None	.	?	.....	Patient in alcoholic coma when admitted to hospital; death 30 hr. after admission

* The following abbreviations are used in describing the lobes involved: R.L.L., lower lobe of the right lung; R.U.L., upper lobe of the right lung; L.L.L., lower lobe of the left lung; R.M.L., middle lobe of the right lung, and L.U.L., upper lobe of the left lung.

† The following abbreviations are used in distinguishing the methods of typing sputum: +M.P., sputum typing obtained from peritoneal fluid of a mouse given an injection of sputum; +M.B., sputum typing obtained from mouse brain culture, and +Sp. sputum typing obtained directly.

§ S.S.S. indicates presence of specific capsular polysaccharide.

‡ The following abbreviations are used in distinguishing therapeutic agents; Sp., sulfapyridine; S., sulfanilamide; Na Sp., i.v., sulfapyridine sodium given intravenously; B.F., B. Friedländer; B.F. A, B. Friedländer A, and B.F. B, B. Friedländer B.

INCIDENCE

In the present series, which included cases from July 1, 1936 through Dec. 31, 1939, there were 2,450 cases of pneumonia, in 37 (1.5 per cent) of which the causative organism was the Friedländer bacillus and in 29 (1.2 per cent) of which it was B. Friedländer A. In 8 (0.5 per cent) of the last 1,750 cases of this series the disease was due to B. Friedländer B. The figures for Friedländer B pneumonia are exclusive of those for the year June 1936 to June 1937, during which time Friedländer B organisms were not typed and classified as such; all Friedländer bacilli not of the A type were left unclassified.

The reported incidence of Friedländer pneumonia varies between 0.4 and 13 per cent. Heffron,[16] in a summary of the findings in three reports, noted an average incidence of 0.5 per cent in a total of 3,319 cases of pneumonia. Bullowa,[17] in a study of 4,416 cases of pneumonia, noted that the cases of Friedländer pneumonia comprised 1.1 per cent of the total. Of 100 cases of pneumonia studied in India by Bhatnagar and Singh,[18] the Friedländer bacillus was the etiologic agent in 13 per cent. Solomon[19] noted an incidence of 0.6 per cent in a review of 5,000 cases, but the incidence was 4.0 per cent in the 300 cases studied carefully.

The relative incidence of Friedländer A pneumonia and Friedländer B pneumonia is similar to that reported by Julianelle, who in his first study[4] reported that the A strain caused 70 per cent of the Friedländer pneumonias. In a later study[20] he showed that in a mixed group of 54 cases of general infections caused by the A and the B strain of B. Friedländer the former was the causative agent in 78 per cent and the latter in 22 per cent; however, of 45 of his cases of Friedländer pneumonias, the A strain was causative in 33, the B strain in 2 and the C strain in 3; in 7 cases the organisms fell into the unclassified group X. Cooper[21] reported that in 95 per cent of cases Friedländer pneumonia

16. Heffron, R.: Pneumonia, with Special Reference to Pneumococcus Lobar Pneumonia, New York, The Commonwelth Fund, 1939.

17. Bullowa, J. G. M.: The Management of the Pneumonias, New York, Oxford University Press, 1937.

18. Bhatnagar, S. S., and Singh, K.: Bacteriological Studies in Acute Lobar Pneumonia Due to Pneumococcus and B. Pneumoniae Friedländer, Indian J. M. Research **23**:337 (Oct.) 1935.

19. Solomon, S.: Primary Friedländer Pneumonia, J. A. M. A. **108**:937 (March 20) 1937.

20. Julianelle, L. A.: The Distribution of Friedländer's Bacilli of Different Types, J. Exper. Med. **52**:539 (Dct.) 1930.

21. Cooper, cited by Solomon,[19] p. 940.

was due to the A strain. In the present series of 37 cases, the A strain was present in 29 (79 per cent) and the B strain in 8 (21 per cent).

Friedländer pneumonia occurs predominantly in older people, as can be readily seen from the following summary:

Series	No. of Patients	Patients Over 40
Bullowa, Chess and Friedman [13]	41	29
Solomon [19]	32	26
Present series	37	26

The mortality is higher in the older age groups, and although the number of cases is insufficient for accurate judgment, there appears to be a tendency for the Friedländer B organism to attack younger persons.

B. Friedländer A	22 patients 40 years or over	(20 died)
	7 patients under 40 years	(5 died)
B. Friedländer B	4 patients 40 years or over	(4 died)
	4 patients under 40 years	(2 died)

As happens in most types of the pneumococcic pneumonias, pneumonia caused by B. Friedländer occurs much more frequently in men than in women. Both Solomon [19] and Bullowa, Chess and Friedman [13] found that seven times as many men as women suffered from Friedländer pneumonia. In the present series of 37 cases, 32 patients were men and 5 were women, a ratio of approximately 7 to 1. However, an interesting fact comes to light when the pneumonia in this series is classified according to type. Of 29 patients with Friedländer A pneumonia 28 were men, a ratio of 28 to 1, and of 8 patients with Friedländer B pneumonia 4 were men and 4 were women, a ratio of 1 to 1.

When the modification of the chi square test especially designed for small samples is applied, there is a high significance for the difference in the ratio of men to women in the A and the B groups, respectively. The probability of the distribution actually observed being due to pure chance is exceedingly small, namely, 0.005, which indicates with practical certainty that there is a definite connection between sex and the occurrence of Friedländer A pneumonia.[22]

BACTEREMIA

In the present study, cultures of the blood were made routinely at the time of the patient's admission to the hospital and were followed, in most cases, by another just before the institution of therapy. Subsequent cultures of the blood were made if the first cultures were positive for the organism, if the patient remained ill or if the patient became worse after admission.

22. Dr. Alfred J. Lotka, of the Metropolitan Life Insurance Co., provided this analysis.

The reported incidence of bacteremia averages about 70 per cent.[23] The general incidence (A and B forms) in the present series was much lower, 32.5 per cent. An interesting difference in tendency to bacteremia in the two types was noted. Seven of the 29 patients with Friedländer A pneumonia (24 per cent) and 5 of the 8 patients with Friedländer B pneumonia (62.5 per cent) had bacteremia.

When the statistical method already used was applied, the probability p was found to be 0.014. Any value for p below 0.05 was considered to be statistically significant. However, the probable error in each group was increased by such factors as the day of illness on which the culture of the blood was made and the number of cultures made. Another fact tending to minimize the significance of the difference was the discrepancy between the low incidence of bacteremia for Friedländer A and B pneumonias as found in this study and that reported by other authors.

TABLE 2.—*Mortality Rates for Friedländer Pneumonias*

Authors	Number of Patients	Percentage of Mortality
Solomon [19]	32	97
Bhatnagar and Singh [18]	13	92
Cole, R. I.: Acute Pulmonary Infections, DeLa Mar Lectures, Johns Hopkins University School of Hygiene and Public Health, 1927-1928	7	71
Bullowa [17]	39	82 *
Bullowa, Chess and Friedman [13]	41	83 †
Present series	37	84

* Untreated patients.
† Untreated and treated patients combined.

MORTALITY

The mortality is consistently high among patients with Friedländer pneumonias. The mortality reported by the various authors is shown in table 2.

The mortality among the patients with Friedländer A and with Friedländer B pneumonia in the present series did not differ significantly, being 86 per cent among the former and 75 per cent among the latter.

Solomon [19] pointed out what is implicit in the data of the other authors cited, namely, that there is no relationship between bacteremia and mortality. (This conclusion may be modified if cultures of the blood are made more frequently.) Indeed, the patients in the present series without bacteremia had a somewhat higher mortality than those with bacteremia. This relationship can be seen in table 3, which also shows the mortality for the two types of Friedländer pneumonia.

23. Bullowa, Chess and Friedman.[13] Bullowa.[17] Solomon.[19]

TREATMENT

Bullowa, Chess and Friedman [18] reported a mortality of 50 per cent for patients with Friedländer A pneumonia who were treated with specific antipneumococcus horse serum. This mortality was contrasted with that of 94 per cent for the untreated patients. All of the 5 patients whom Solomon [19] treated with horse serum died. However, Solomon used smaller amounts of serum in all but 1 case, and therefore the results

TABLE 3.—*Mortality Rates for Two Types of Friedländer Pneumonia, Both With and Without Bacteremia, in Present Series*

	Number of Patients	Number Died	Percentage of Mortality
Friedländer A pneumonia			
Bacteremia	7	6	86
No bacteremia	22	19	86
Total	29	25	86
Friedländer B pneumonia			
Bacteremia	5	3	60
No bacteremia	3	3	100
Total	8	6	75
Combined group (Friedländer A and Friedländer B pneumonias)			
Bacteremia	12	9	75
No bacteremia	25	22	88
Total	37	31	84

TABLE 4.—*Results of Treatment of Friedländer A and B Pneumonias in Present Series*

	SP.*		SP.* and Serum		Serum Alone		No Treatment	
	Patients	Deaths	Patients	Deaths	Patients	Deaths	Patients	Deaths
Friedländer A Pneumonia								
Total	8	5	2	2	13	13	6	5
Without bacteremia	6	4	2	2	9	9	5	4
With bacteremia	2	1	0	0	4	4	1	1
Friedländer B Pneumonia								
Total	1	1	5	4	.....		2	1
Without bacteremia	0	0	2	2	.....		1	1
With bacteremia	1	1	3	2	.....		1	0

* SP. indicates sulfanilamide or sulfapyridine, as indicated in table 1.

are not comparable. The results of the therapy in the present series, including those in patients treated with sulfanilamide or sulfapyridine, are shown in table 4.

Of 23 treated patients with Friedländer A pneumonia, 6 of whom had bacteremia, 20 died, and of 6 untreated patients, 1 of whom had bacteremia, 5 died.

Of the patients with Friedländer A pneumonia treated with serum alone, 3 received rabbit serum and 10 horse serum. All these patients

died. However, if there is any greater advantage in the use of rabbit serum, it could not be ascertained from this group, since those patients who were given rabbit serum died too soon after admission to have received an adequate amount.

Of 6 treated patients with Friedländer B pneumonia, 4 of whom had bacteremia, 5 died, and of 2 untreated patients, 1 of whom had bacteremia, the patient without bacteremia died. The details of therapy are given in table 1.

Administration of serum, sulfanilamide (or sulfapyridine) or the two combined seemed ineffectual in treating patients with B. Friedländer pneumonia in our series. Indeed, among the patients with Friedländer B pneumonia, the mortality of the treated ones was 83 per cent and the mortality of the untreated ones 50 per cent. One hopeful trend could be seen in the patients with Friedländer A pneumonia, for treatment with the drug was accompanied by recovery in 3 of 8 cases.

COMMENT

That there is no relationship between bacteremia and mortality was indicated in Solomon's report and in the present study. Baehr, Shwartzman and Greenspan [15] reported transient bacteremia from the genitourinary tract and elsewhere in patients who recovered spontaneously. It was shown [24] that the presence of specific capsular polysaccharide in the blood stream of patients with pneumococcic pneumonia has a far more serious prognosis than the finding of bacteremia alone in such patients, especially in pneumonias caused by Pneumococcus type III. The Friedländer bacillus, like the type III pneumococcus, has a huge capsule and produces much polysaccharide. These facts suggest that in cases of Friedländer pneumonia, the presence of a small or avirulent focus with the simple transient occurrence of bacteremia is relatively innocuous as compared with the presence of a large or virulent focus of infection, with or without the occurrence of bacteremia.

Several observers [16] expressed the opinion that even the relatively low incidence reported for pneumonia due to Friedländer bacillus is too high, because the organism is a frequent contaminant and therefore is too often erroneously considered the etiologic agent. In Solomon's experience the reported incidence is too low. That the Friedländer bacillus is not a preagonal invader or a postmortem contaminant is amply borne out by the fact that, without exception, we have never found

24. Bullowa, J. G. M.; Bukantz, S. C., and de Gara, P. F.: The Balance Between Capsular Polysaccharide and Antibody in Relation to the Prognosis and Therapy of Pneumococcal Pneumonia, Ann. Int. Med. **14**:1348 (Feb.) 1941. Bullowa, Bukantz and de Gara.[7a]

Friedländer organisms in many hundreds of preagonal and postmortem cultures of the blood and of puncture fluid from the lungs. Nor has this bacillus, in our experience, been found as a contaminant in cultures taken from lung tissue at the autopsy table. We have had one epidemic of infections caused by Friedländer bacillus in the mice used for sputum typing, which resulted in a few false diagnoses, but it was quickly apprehended and the diagnoses corrected.

The success of serum therapy depends on the early administration of a "sufficient" amount of specific serum. Certain of the types of pneumococci, for example types II and III, produce large amounts of specific capsular polysaccharide; successful serum therapy of pneumonias caused by these types depends on the administration of comparatively larger amounts of serum than is required for pneumonias caused by the other types. Reasoning by analogy, we assumed that since Friedländer organisms produce a large amount of specific capsular polysaccharide, the treatment of infections caused by B. Friedländer requires relatively larger amounts of serum to neutralize this substance. Indeed, the relatively massive amounts of serum given in several of the aforementioned cases may have been ineffectual because they were still insufficient. Certainly, the amount of type II antipneumococcus serum given in the case of Friedländer pneumonia reported was insufficient, unless it was just the amount needed to supplement the effect of the sulfapyridine and the patient's own immunity and so swing the balance in favor of the host.

Only 2 patients with chronic Friedländer pneumonia were seen, 1 recorded as case 17 and another not included in the series because he was admitted to the service after January 1940. Both patients had mild diabetes. These were the only patients with diabetes in the series. Both died with extensive cavitations.

SUMMARY

A case of Friedländer B pneumonia with apparent cure is reported. Therapy is discussed.

A review of 37 cases of pneumonia due to Friedländer bacillus is presented, and the available statistics are summarized.

B. Friedländer B is immunologically related to Pneumococcus type II, and type II antipneumococcus serum may be of value in the specific treatment of Friedländer B pneumonia.

The lack of relationship of bacteremia to mortality is pointed out.

The inadequency of the various forms of therapy used is noted.

The Friedländer organism, in our experience, is not a contaminant or a preagonal invader.

Seven times as many men as women have Friedländer pneumonia. However, the ratio of men to women with Friedländer A pneumonia is 28 to 1, as compared with the ratio for Friedländer B pneumonia, which is 1 to 1. This is a statistically significant difference in sex incidence. The incidence of bacteremia is probably significantly higher in cases of Friedländer B pneumonia than in those of Friedländer A pneumonia. The differentiation between Friedländer A and Friedländer B pneumonia should always be made in the interest of a better understanding of the disease and the institution of more rational therapy.

USE OF SULFANILAMIDE AND SULFAPYRIDINE IN THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS

MEYER FRIEDMAN, M.D.
WITH THE COLLABORATION OF ARTHUR SELZER, M.D., AND PATRICIA McLEAN, B.A.
SAN FRANCISCO

With the introduction of the original prontosil (the hydrochloride of 4-sulfamido-2', 4'-diaminoazobenzene) by Domagk [1] and the confirmation of the action of sulfanilamide and its derivatives by other observers,[2] a new era in chemotherapy was begun. The discovery of sulfanilamide as the effective principle in the prontosil molecule and the widespread use of this drug in treatment of infections other than those due to the hemolytic streptococcus quickly followed. A further impetus was given to progress in this renascent field in 1938 by the clinical introduction of sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine) by Whitby,[3] who demonstrated its striking efficacy in treatment not only of infections due to the pneumococcus but also of those due to the hemolytic streptococcus. These initial observations of Whitby, like those of Domagk, were quickly and amply confirmed in the last several years by numerous workers.[4]

From the Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital.

1. Domagk, G.: Ein Beitrag zur Chemotherapie der bakteriellen Infektionen, Deutsche med. Wchnschr. **61**:250, 1935.

2. Levaditi, C., and Vaisman, A.: Action curative et préventive du chlorhydrate de 4-sulfamido-2, 4-diamino-azobenzène dans l'infection streptococcique expérimentale, Compt. rend. Acad. d. sc. **200**:1694, 1935. Colebrook, L., and Kenny, M.: Treatment of Human Puerperal Infections and of Experimental Infections in Mice with Prontosil, Lancet **1**:1279, 1936. Buttle, G. A. H.; Gray, W. H., and Stephenson, D.: Protection of Mice Against Streptococcal and Other Infections by *p*-Aminobenzenesulphonamide and Related Substances, ibid. **1**:1286, 1936. Long, P. H., and Bliss, E. A.: Use of *p*-Aminobenzene Sulphonamide (Sulfanilamide) or Its Derivatives in the Treatment of Infections Due to Beta Hemolytic Streptococci, Pneumococci and Meningococci, South. M. J. **30**:479, 1937. Mellon, R. R.: New Approach to Therapeusis of Hemolytic Streptococcal Infections, Proc. Soc. Exper. Biol. & Med. **34**:474, 1936.

3. Whitby, L. E. H.: Chemotherapy of Pneumococcal and Other Infections with 2-(*p*-Aminobenzenesulphonamido) Pyridine, Lancet **1**:1210, 1938.

4. Evans, G. M., and Gaisford, W. F.: Treatment of Pneumonia with 2-(*p*-Aminobenzenesulphonamido) Pyridine, Lancet **2**:14, 1938. Telling, M., and

(Footnote continued on next page)

Despite this rapid advance in the treatment of various infectious diseases, the fundamental mode of action of both of these drugs is still not completely understood. For there were those [5] who expressed the belief that sulfanilamide, and by inference sulfapyridine, too, changes into some more powerful compound within the body; others [6] stated the opinion that these drugs may act by the potentiation of tissue resistance to invasion by bacteria and thus act to combat effectively specific infections. But it would seem at the present writing that the majority of observers [7] have concluded that the action of the drug is fundamentally exercised directly on the micro-organism and consists of the partial destruction or inhibition of the proliferation of the organism. Further, they suggested that in general the in vivo and the in vitro actions of these drugs are essentially similar.

Undoubtedly, as Long and Bliss pointed out in their excellent monograph,[7a] many of the discrepancies present in the literature concerning the mode of action of these drugs were probably due to differences in environmental conditions present in the studies, for it has been shown that their action is a variable function which is dependent to a great degree on environmental factors, such as temperature control, the type of medium used, the presence or absence of peptone in the medium, the type and strain of organism used, the duration of the experiment and, finally, the size of the initial inoculum of bacteria which are being tested. Then, too, the inability of investigators to evaluate the in vivo action of sulfanilamide or sulfapyridine in the absence of any possible direct

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Oliver, W. A.: Case of Massive Pneumonia with Massive Collapse, Treated with 2-(*p*-Aminobenzenesulphonamido) Pyridine, ibid. **1**:1391, 1938. Flippin, H., and Pepper, D. S.: Use of 2-(*p*-Aminobenzenesulphonamido) Pyridine in the Treatment of Pneumonia, Am. J. M. Sc. **196**:509, 1938.

5. Levaditi, C., and Vaisman, A.: La chimiothérapie antiendotoxique, Ann. Inst. Pasteur **61**:635, 1938. Mayer, R. L.: Recherches sur le mécanisme de l'action antistreptococcique de l'amino-benzènesulfamide et de ses dérivés, Bull. Acad. de méd., Paris **117**:727, 1937. Locke, A.; Main, E. R., and Mellon, R. R.: Anti-Catalase and the Mechanism of Sulfanilamide Action, Science **88**:620, 1938.

6. McKinney, R. A., and Mellon, R. R.: Sulfanilamide and Macrophage Response to Hemolytic Streptococci in Mice, Proc. Soc. Exper. Biol. & Med. **37**: 333, 1937. Finklestone-Sayliss, H.; Paine, C. G., and Patrick, L. B.: Bacteriostatic Action of *p*-Aminobenzenesulphonamide upon Hemolytic Streptococci, Lancet **2**:792, 1937.

7. (*a*) Long, P. H., and Bliss, E. A.: Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillan Company, 1939. (*b*) Gay, F. P., and Clark, A. R.: On the Mode of Action of Sulfanilamide in Experimental Empyema, J. Exper. Med. **66**:535, 1937. (*c*) Levaditi, C.: La chimiothérapie des infections microbiennes. Son mécanisme d'action, Schweiz. Ztschr. f. allg. Path. u. Bakt. **1**:365, 1938. (*d*) MacMahon, B. J.: Influence of Sulfanilamide on Infected Sinuses of Rabbits: Chemical and Microscopic Studies, Arch. Otolaryng. **28**:222 (Aug.) 1938.

interference by the animal's own tissue has of course been partially responsible for the obscurity surrounding the mode of action of these drugs.

Despite the vast amount of work that has been done in relation to the effect and mode of action of these two drugs on the hemolytic streptococcus, the pneumococcus and other organisms, relatively little work has been reported concerning their possible mode of action and their effect on Streptococcus viridans under controlled conditions, and the reports that are available are contradictory and rather vague. Thus, Long and Bliss [8] reported that sulfanilamide in concentrations of $\frac{1}{10,000}$ markedly inhibited the growth of the alpha hemolytic streptococcus. However, Britton [9] tested three strains of Str. viridans and found that two were unaffected by a concentration of sulfanilamide as high as $\frac{1}{500}$ and the third strain was inhibited in its growth only when the concentration of sulfanilamide was as high as $\frac{1}{1,000}$. Further, Maegraith and Vollum [10] found that sulfanilamide and sulfapyridine acting in defibrinated blood previously deprived of leukocytes had no measurable effect on Str. viridans, but if these same experiments with blood were repeated in the presence of leukocytes it was found that a concentration of either drug as low as $\frac{1}{60,000}$ would effect bacteriostasis. The studies cited were all made in vitro, and there have been no in vivo experiments concerning the effect of these drugs on Str. viridans, for, as Whitby [11] has pointed out, inability to produce an infection with this organism in the experimental animal has made it impossible to determine the in vivo efficacy of either sulfanilamide or sulfapyridine on Str. viridans under controlled conditions.

Likewise, there have also been few reports concerning the use of either drug in the treatment of the clinical entity subacute endocarditis caused by Str. viridans, and, as previously noted with reference to the experimental observations, the results are conflicting. Thus, although there are scattered reports [12] of cures obtained in cases of subacute endocarditis after the administration of sulfanilamide, the majority of

8. Long, P. H., and Bliss, E. A.: Para-Amino-Benzene-Sulfonamide and Its Derivatives, J. A. M. A. **108**:32 (Jan. 2) 1937.

9. Britton, C. J. C.: The Effect of Sulphonamide Compounds on Certain Bacteria in Vitro, Brit. J. Exper. Path. **19**:140, 1938.

10. Maegraith, B. G., and Vollum, R. L.: The Bacteriostatic Effects of Sulphonamide-P, Soluseptasine, and M & B 693, Brit. M. J. **2**:985, 1938.

11. Whitby, L. E. H.: Chemotherapy of Bacterial Infections, Lancet **2**:1095, 1938.

12. Major, R. H., and Leger, L. H.: Recovery from Subacute Infectious Endocarditis Following Prontosil Therapy, J. A. M. A. **111**:1919 (Nov. 19) 1938. Long and Bliss.[7a]

reports [13] concerning the efficacy of sulfanilamide are extremely pessimistic. With the possible exception of the cases reported by Kelson and White,[14] who treated their patients with sulfapyridine and heparin, no report could be found which indicated that sulfapyridine was of any real aid in the treatment of subacute endocarditis, but several reports [15] have been published concerning its seeming inefficacy in the treatment of this disease.

Although it may be only of scientific interest to determine in infections caused by the hemolytic streptococcus or pneumococcus whether sulfanilamide and sulfapyridine act directly on the invading microorganism or act to increase the tissue resistance against the invasion, it becomes of the utmost practical importance in the consideration of any chemotherapeutic approach to the disease subacute endocarditis to determine the exact mode of action of the drugs concerned. For this disease has been shown [16] to be unlike the ordinary infection caused by a hemolytic streptococcus in that it is primarily a focus of growing, relatively avirulent streptococci in a fibrin-platelet mass which not only completely isolates the organisms contained within it from the living tissue of the body (circulating as well as fixed) but also may act to prevent them from coming into contact with any particular chemical substance which may be introduced into the blood stream. Accordingly, if sulfanilamide or sulfapyridine, or any other drug for that matter, is to be effective in the treatment of this disease, this drug must not only be able to destroy or markedly inhibit the growth of Str. viridans without the physical aid of living tissue but, just as important, also be able to penetrate the fibrin-platelet barrier, characteristic of this disease, in sufficient concentration to effect its results. Conversely, if a drug depends on the potentiation of living tissue resistance for its effective-

13. Klee, P. H., and Römer, H.: Prontosil bei Streptokokkenerkrankungen, Deutsche med. Wchnschr. **61**:253, 1940. Spink, W. W., and Crago, F. H.: Evaluation of Sulfanilamide in the Treatment of Patients with Subacute Endocarditis, Arch. Int. Med. **64**:228 (Aug.) 1939. Sailer, S.: Subacute Bacterial Endocarditis Treated with Sulfanilamide Resulting in Granulocytopenia and Death, Am. J. Clin. Path. **9**:269, 1939. Fuge, K.: Die Behandlung der Puerperalsepsis mit Prontosil, Deutsche med. Wchnschr. **61**:1672, 1935.

14. Kelson, S. R., and White, P. D.: New Method of Treatment of Subacute Bacterial Endocarditis, Using Sulfapyridine and Heparin in Combination, J. A. M. A. **113**:1700 (Nov. 4) 1939.

15. Ellis, G. R.: Treatment of Subacute Bacterial Endocarditis with M. & B. 693, Lancet **2**:1521, 1938. Long and Bliss.[7a] Whitby.[11]

16. (*a*) Friedman, M.; Katz, L. N., and Howell, K.: Experimental Endocarditis Due to Streptococcus Viridans: Biologic Factors in Its Development, Arch. Int. Med. **61**:95 (Jan.) 1938. (*b*) Friedman, M.: A Study of the Fibrin Factor in Relation to Subacute Endocarditis, J. Pharmacol. & Exper. Therap. **63**: 173, 1938.

ness or if it is unable to penetrate a physicochemical barrier in sufficient amount to eradicate or inhibit the growth of organisms protected by this barrier, it will probably be of no value in the treatment of an infection that is so routinely characterized by its isolation from living tissue and its physicochemical barriers to therapeutic accessibility.

With a view to studying sulfanilamide and sulfapyridine and their properties in the light of the principles discussed, a series of experiments and observations were executed to determine (1) the degree of penetrability of both drugs through fibrin-platelet masses, (2) the in vitro effects of both drugs on three different strains of Str. viridans, (3) the in vivo effects of both drugs on animals harboring these three strains of Str. viridans but with the complete isolation of the microorganisms from the living tissue of the animal, (4) the effects of the prolonged administration of both drugs on the persistence of an infection artificially induced by Str. viridans within an animal and, finally, (5) the actual results obtained with the administration of both of these drugs to patients suffering with subacute endocarditis due to Str. viridans. From these experiments and observations, it was thought that a definitive evaluation of the effect of sulfanilamide and sulfapyridine in the treatment of subacute endocarditis could be made. Further, it was thought that the experiments allowed for the first time a direct comparison between the in vitro and the in vivo effects of the drugs without the final results being obscured by the complicating effects of interference by living tissue.

I. PERMEABILITY OF FIBRIN MASSES TO SULFANILAMIDE AND SODIUM SULFAPYRIDINE

Method.—For this study, an apparatus previously designed and described [16b] was used which allowed the determination of the penetrability of a fibrin membrane by sulfanilamide and sulfapyridine. The mass itself was made by rotating a stirring rod in freshly drawn dogs' blood and then removing the fibrin-platelet membrane formed around the rod immersed in the blood. This membrane was cut to appropriate size and inserted between the two glass cylinders of the apparatus and was always tested for gross leaks at the beginning and at the end of any experiment. If no initial leak was present, sulfanilamide or sulfapyridine in varying concentrations was added to one cylinder (cylinder 1) and a physiologic solution of sodium chloride was added to the other (cylinder 2). At intervals, a small sample was removed from the cylinder originally containing only physiologic solution of sodium chloride and was tested for sulfanilamide or sulfapyridine, whichever was being used. The capacity of each cylinder was 3 cc., and the diameter of the fibrin barrier was 5 mm.

Results.—Inspection of table 1 shows clearly that the rate of diffusion of either drug through a fibrin membrane is not constant, but in no experiment was there even 50 per cent diffusion of either drug through the thinnest of membranes in twenty-four hours. When it is considered that a vegetation is many millimeters in thickness and that rarely is the sulfanilamide or sulfapyridine at a constant level

of 10 to 20 mg. per hundred cubic centimeters of blood over many days, it can easily be seen that it is questionable whether an effective amount of either drug could ever reach the interior of a vegetation and render it sterile. This might well explain the frequent clinical observation that the disease apparently progresses despite a negative blood culture.

II. EFFECT OF SULFAPYRIDINE ON THE GROWTH OF STR. VIRIDANS

Method.—Since our primary object was to study the effect of parenterally administered sulfanilamide and sulfapyridine acting without the aid of any possible influence of living tissue, a means had to be effected for introducing the streptococci in the body of the animal, yet isolating them from any actual physical contact

TABLE 1.—*Diffusion of Sulfanilamide and Sodium Sulfapyridine Through a Fibrin Mass*

Initial Concentration of Drug in Cylinder, Mg. per 100 Cc.	Thickness of Fibrin Membrane, Mm.	Concentration of Drug in Cylinder 2, Mg. per 100 Cc.			
		1 Day	3 Days	6 Days	9 Days
		Sulfanilamide			
500	1.0	32.0	....	...	...
500	1.0	26.0	....	...	...
100	1.0	6.5	....	...	...
100	1.0	19.0	....	...	...
100	1.0	10.0	23.0	...	...
20	1.0	3.0	10.0	...	...
20	1.0	4.0	10.0	...	...
10	1.0	1.0	3.0	...	...
10	2.0	0.5	0.5	...	...
		Sodium Sulfapyridine			
50	3.0	0.5	7.0	...	...
20	1.5	...	0.5	2.0	6.0
20	6.0	...	0.5	3.0	6.0

with living tissue. For this purpose, porcelain filters (two to three) of 10 cc. capacity were devised, the open end of which could be sealed with a rubber cap, which was then dipped in paraffin, the filters thus being made completely leak proof. Also, because the in vivo action of sulfanilamide was to be compared with its in vitro action under the same environmental conditions, glass containers open at one end were fitted with rubber caps and sealed completely with paraffin.

A preliminary series of experiments was performed with these porcelain filter capsules in order to determine the amount of parenterally given sodium sulfapyridine which would enter the interior of the capsule and the time factor which was involved. It was found that if the porcelain capsules were inserted into the peritoneal cavities of rabbits and 0.5 Gm. of sodium sulfapyridine was given intravenously every two hours to these rabbits, at the end of six hours the average concentration of sodium sulfapyridine in a capsule was 4.9 mg. per hundred cubic centimeters (eight experiments). It was found that if the capsules were initially filled with a solution containing a concentration of sodium sulfapyridine of 5 mg. per hundred cubic centimeters and then placed in the abdomens of rabbits who later received no sulfapyridine, at the end of six hours the concentration had fallen

to 3.8 mg. per hundred cubic centimeters (four experiments). Thus, it was found that a transfer of sulfapyridine could occur in either direction, that is, either from the body fluids into the capsule or from the capsule to the body fluids.

Three strains of organisms identified as Str. viridans [17] were used in these experiments; two of them were isolated from patients who were suffering from subacute endocarditis and the course of whose illness is reported later in this article. The procedure consisted of obtaining 1 cc. of a twenty-four hour dextrose broth culture, making a $\frac{1}{100}$ dilution and then adding 1 cc. of the dilution to 100 cc. of a dog serum–dextrose broth mixture (50 per cent of each). Three different studies were made on each strain, with the exception of strain H. In general, six capsules were filled completely with the serum–Str. viridans–dextrose broth mixture. Two glass containers were also filled with the same mixture plus enough sodium sulfapyridine to give a concentration of 5 mg. per hundred cubic centimeters. Then 4 rabbits were anesthetized, their abdomens were opened, and 3 of these rabbits received two filter capsules each and the fourth rabbit the two glass containers. Two of the 3 rabbits receiving filter capsules then received 0.5 Gm. of sodium sulfapyridine intravenously every two hours until 3 Gm. of the drug had been given at the end of ten hours. Then injections were omitted for eight hours and again resumed every two hours, until at the end of twenty-four hours each animal had thus received a total of 4.0 to 4.5 Gm. of sodium sulfapyridine. The remaining rabbit receiving the filter capsules was given no sulfapyridine, and these capsules served as a control. Likewise, the animal containing the two glass tubes received no sodium sulfapyridine except that placed initially in the tube. Rectal temperatures were uniformly taken about eight hours after the insertion of the capsules. At the end of twenty-four hours the animals' abdomens were incised, the capsules were removed and opened, the fluid was removed under aseptic conditions and bacterial counts, determination of the sulfapyridine content and direct inoculation of blood agar were made. In the second series, reported under subsection B, the same procedure was carried out except that the mixture placed in four of these filter capsules contained 5 mg. per hundred cubic centimeters of sodium sulfapyridine; the remaining two filter capsules contained no sodium sulfapyridine and were inserted into a rabbit who also received no sulfapyridine; thus they served as the control. In the third series, reported under subsection C, the same procedure was followed except that four of the filter capsules contained 10 mg. per hundred cubic centimeters of sodium sulfapyridine; the remaining two filter capsules still contained no sulfapyridine and served as the control.

Results.—A. Effect of Sulfapyridine (parenterally administered) on Str. Viridans: As can readily be seen from table 2, although all the filter capsules placed in the animals receiving sodium sulfapyridine intravenously had a significant concentration of sulfapyridine within them at the end of twenty-four hours, there was relatively little effect of this administered sodium sulfapyridine on the growth of any of the three strains when compared with the growth within the control filter capsules contained in the abdomens of rabbits receiving no sulfapyridine. The marked bactericidal action of the sodium sulfapyridine acting in the glass tubes, which was in reality an in vitro experiment, appears at first paradoxic in the light of various investigations which have demonstrated that the in vivo action of sulfapyridine was as strong as, or perhaps stronger than, its in vitro action. However, as has already been mentioned, at least six hours must elapse before

17. Dr. Lowell Rantz, of Stanford University School of Medicine, determined the identity of the three strains used in these experiments.

TABLE 2.—*Effect of Parenteral Administration of Sodium Sulfapyridine on Str. Viridans*

Rabbit	Type of Container Introduced Within Rabbit's Abdomen *	Initial Sodium Sulfapyridine in Container, Mg. per 100 Cc.	Total Parenteral Administration of Sodium Sulfapyridine, Gm.	Sulfapyridine in Container After 24 Hours, Mg. per 100 Cc.	Initial Number of Streptococci Added to Container	Number of Streptococci in Container After 24 Hours	Temperature (C.) of Rabbit 8 Hours After Operation	Growth of Container Fluid on Blood Agar	Duration of Experiment, Hours
	Strain H								
1	Filter capsules Ia	0	4.5	6.0	1.2×10^8	1.0×10^{11}	40.0	++++	24
	Filter capsules IIa	0	4.5	5.8	1.2×10^8	2.8×10^{11}	40.0	++++	24
2	Filter capsules Ib	0	4.5	7.2	1.2×10^8	6.0×10^{10}	39.8	++++	24
	Filter capsules IIb	0	4.5	4.5	1.2×10^8	1.7×10^{11}	39.8	++++	24
3	Glass capsules Ic	5	0	5.0	1.2×10^8	$<1 \times 10^5$ †	40.0	+	24
	Glass capsules IIc	5	0	4.6	1.2×10^8	$<1 \times 10^5$ †	40.0	+	24
4	Filter capsules Id (control)	0	0	0	1.2×10^8	3×10^{11}	39.6	++++	24
	Filter capsules IId (control)	0	0	0	1.2×10^8	1.5×10^{11}	39.6	++++	24
	Strain R								
1	Filter capsules Ia	0	4.5	4.5	1.5×10^8	3.2×10^{10}	39.2	++++	24
	Filter capsules IIa	0	4.5	4.2	1.5×10^8	3.5×10^{10}	39.2	++++	24
2	Filter capsules Ib	0	4.5	3.8	1.5×10^8	1.2×10^{11}	39.6	++++	24
	Filter capsules IIb	0	4.5	5.0	1.5×10^8	2.0×10^{11}	39.6	++++	24
3	Glass capsules Ic	5	0	4.8	1.5×10^8	$<1.0 \times 10^8$ †	39.0	+	24
	Glass capsules IIc	5	0	4.8	1.5×10^8	$<1.0 \times 10^8$ †	39.0	+	24
4	Filter capsules Id (control)	0	0	0	1.5×10^8	4.2×10^{11}	39.4	++++	24
	Filter capsules IId (control)	0	0	0	1.5×10^8	2.5×10^{11}	39.4	++++	24
	Strain S								
1	Filter capsules Ia	0	4.5	4.2	1.5×10^8	8.8×10^{10}	39.8	++++	24
	Filter capsules IIa	0	4.5	5.0	1.5×10^8	4.0×10^{10}	39.8	++++	24
2	Filter capsules Ib	0	4.5	3.5	1.5×10^8	1.2×10^{11}	39.2	++++	24
	Filter capsules IIb	0	4.5	7.2	1.5×10^8	1.2×10^{11}	39.2	++++	24
3	Glass capsules Ic	5	0	4.8	1.5×10^8	$<1.0 \times 10^4$ †	39.0	0	24
	Glass capsules IIc	5	0	4.9	1.5×10^8	$<1.0 \times 10^4$ †	39.0	0	24
4	Filter capsules Id (control)	0	0	0	1.5×10^8	5.4×10^{11}	39.6	++++	24
	Filter capsules IId (control)	0	0	0	1.5×10^8	3.2×10^{11}	39.6	++++	24

* As indicated in this table and in tables 3, 4 and 5, two capsules were introduced into each rabbit.
† Dilutions for counting were begun at this level.

the parenterally administered sulfapyridine enters the filter capsule in sufficient quantity to effect a significant concentration, so that during this lag period of six hours the growth of the organism may have easily taken place. Accordingly, it was decided to introduce into the filter capsules to be placed in sulfapyridine-treated animals enough sulfapyridine from the very beginning to effect a significant concentration during the first six hours and until the parenterally administered sulfapyridine entered in sufficient concentration.

B. Effect of Parenterally Administered Sulfapyridine on Str. Viridans When Sulfapyridine Was Initially Introduced Within the Filter and Glass Capsules (concentration of 5 mg. per hundred cubic centimeters):

As can be seen in table 3, there was in all filter capsules in treated rabbits, regardless of the strain, a marked reduction in bacterial growth as compared to that in the control filter capsules inserted into untreated rabbits. Indeed, as table 3 indicates, in three of the filter capsules containing streptococci of the strain R variety there was complete sterilization, and in all filter capsules placed in treated animals there was not only bacteriostasis but actually partial sterilization, since the total number of bacteria present after twenty-four hours was less than the number added. It is of interest to note that in no strain was the in vivo action of parenterally administered sulfapyridine any more effective than the in vitro action of the sulfapyridine in the glass containers. It would seem, therefore, that the in vivo action of sulfapyridine on Str. viridans differs in no respect from its in vitro action when living tissue is not in actual contact with the organism. This last factor may be of importance in the attack by these drugs on other organisms, but, as already mentioned, in the vegetative endocarditis caused by Str. viridans there is no living tissue in actual contact with the organism.

C. Effect of Parenterally Administered Sodium Sulfapyridine on Str. Viridans When Sulfapyridine Was Initially Introduced Within the Filter and Glass Capsule (concentration of 10 mg. per hundred cubic centimeters):

As table 3 indicates, the same bactericidal effect was observed on the two strains tested as was previously found when the initial sodium sulfapyridine concentration was 5 mg. per hundred cubic centimeters. In this group, too, it will be observed that the in vivo action of sodium sulfapyridine was no more effective than that observed within the glass containers. But it is important to point out that whether sodium sulfapyridine was acting in the glass container or in the filter capsule, having wandered from the blood stream, its action was potent and decidedly effective under these conditions and appeared adequate in itself.

III. EFFECT OF SULFANILAMIDE ON THE GROWTH OF STR. VIRIDANS

Since the action of sodium sulfapyridine was found to be so remarkably effective on the growth of Str. viridans if the inoculums were small and if the sulfapyridine was administered at once, it was considered advisable to test the action of sulfanilamide on the same three strains of Str. viridans in the same manner.

Methods.—Exactly the same technic was used in this group of experiments as was used in the experiments with sulfapyridine, except that sulfanilamide instead of sodium sulfapyridine was initially introduced into the filter capsules and glass capsules placed in animals treated with sulfanilamide. Two sets of experiments were carried out, the first with an initial concentration of sulfanilamide of 5 mg. per hundred cubic centimeters in the appropriate filter and glass capsules, the

TABLE 3.—*Effect of the Parenteral Administration of Sulfapyridine on the Growth of Str. Viridans with Introduction of Sulfapyridine into Capsules before Peritoneal Implantation*

Rabbit	Type of Container Introduced	Initial Sodium Sulfapyridine in Container, Mg. per 100 Cc.	Total Parenteral Administration of Sodium Sulfapyridine, Gm.	Sulfapyridine in Container After 24 Hours, Mg. per 100 Cc.	Initial Number of Streptococci Added to Container	Number of Streptococci in Container After 24 Hours	Temperature (C.) of Rabbit 8 Hours After Operation	Growth of Container Fluid on Blood Agar	Duration of Experiment, Hours
				Strain H					
1	Filter capsules Ia	5	4.0	4.0	2.0×10^7	1.4×10^5	39.4	++	24
	Filter capsules IIa	5	4.0	5.0	2.0×10^7	9×10^4	39.4	+	24
2	Filter capsules Ib	5	4.0	4.0	2.0×10^7	1.1×10^5	39.0	++	24
	Filter capsules IIb	5	4.0	...	2.0×10^7	.....	39.0	—	24
3	Glass containers Ic	5	0	5.0	2.0×10^7	1.4×10^5	39.6	++	24
	Glass containers IIc	5	0	5.0	2.0×10^7	2.1×10^5	39.6	++	24
4	Filter capsules Id	10	4.0	11.0	2.0×10^7	$<1 \times 10^3$ *	39.0	+	24
	Filter capsules IId	10	4.0	7.6	2.0×10^7	4×10^3	39.0	++	24
5	Filter capsules Ie	10	4.0	5.0	2.0×10^7	8×10^4	40.2	++	24
	Filter capsules IIe	10	4.0	5.0	2.0×10^7	4×10^5	40.2	+	24
6	Glass containers If	10	0	10.0	2.0×10^7	2×10^5	39.6	++	24
	Glass containers IIf	10	0	10.0	2.0×10^7	1×10^5	39.6	++	24
7	Filter capsules Ig (control)	0	0	0	2.0×10^7	1.3×10^{11}	39.4	++++	24
	Filter capsules IIg (control)	0	0	0	2.0×10^7	4.2×10^{11}	39.4	++++	24
				Strain R					
8	Filter capsules Ia	5	4.0	10.1	1.5×10^8	$<1 \times 10^5$ *	39.0	+	24
	Filter capsules IIa	5	4.0	11.0	1.5×10^8	$<1 \times 10^5$ *	39.0	0	24
9	Filter capsules Ib	5	4.0	11.2	1.5×10^8	$<1 \times 10^5$ *	39.2	0	24
	Filter capsules IIb	5	4.0	10.0	1.5×10^8	$<1 \times 10^5$ *	39.2	0	24
10	Glass containers Ic	5	0	5.0	1.5×10^8	$<1 \times 10^5$ *	39.0	0	24
	Glass containers IIc	5	0	5.0	1.5×10^8	$<1 \times 10^5$ *	39.0	0	24
11	Filter capsules Id	10	4.5	12.0	1.5×10^8	$<1 \times 10^3$ *	40.2	+	24
	Filter capsules IId	10	4.5	15.6	1.5×10^8	$<1 \times 10^3$ *	40.2	+	24
12	Filter capsules Ie	10	4.5	14.2	1.5×10^8	$<1 \times 10^3$ *	39.6	+	24
	Filter capsules IIe	10	4.5	13.8	1.5×10^8	$<1 \times 10^3$ *	39.6	+	24
13	Glass containers If	10	0	9.0	1.5×10^8	$<1 \times 10^3$ *	39.2	0	24
	Glass containers IIf	10	0	10.2	1.5×10^8	$<1 \times 10^3$ *	39.2	+	24
14	Filter capsules Ig (control)	0	0	0	1.5×10^8	6.0×10^{11}	39.0	++++	24
	Filter capsules IIg (control)	0	0	0	1.5×10^8	4.7×10^{11}	39.0	++++	24
				Strain S					
15	Filter capsules Ia	5	4.0	5.0	1.4×10^8	1.3×10^5	40.5	++	24
	Filter capsules IIa	5	4.0	5.1	1.4×10^8	1.5×10^5	40.5	++	24
16	Filter capsules Ib	5	4.0	6.5	1.4×10^8	4.0×10^4	39.0	+	24
	Filter capsules IIb	5	4.0	7.5	1.4×10^8	1.0×10^5	39.0	+	24
17	Glass containers Ic	5	0	5.0	1.4×10^8	$<1.0 \times 10^3$ *	39.5	+	24
	Glass containers IIc	5	0	5.0	1.4×10^8	$<1.0 \times 10^3$ *	39.5	+	24
18	Filter capsules Id (control)	0	0	0	1.4×10^8	1.8×10^{11}	39.3	++++	24
	Filter capsules IId (control)	0	0	0	1.4×10^8	2.5×10^{11}	39.3	++++	24

* Dilutions for counting were begun at this level.

second with an initial concentration of sulfanilamide of 10 mg. in similar capsules. All filter capsules placed in untreated rabbits of course contained no sulfanilamide and served as controls. The rabbits were placed on the same schedule of injections as the sodium sulfapyridine-treated animals, except that the injections were given both intravenously and subcutaneously—approximately 10 cc. of a 1 per cent solution of sulfanilamide intravenously and 50 to 80 cc. of a 1 per cent solution of sulfanilamide subcutaneously at each injection. In some animals, this tremendous dose had to be reduced, as can be seen by inspection of table 4. As in the experiments with sodium sulfapyridine, the capsules were removed after twenty-four hours and studied in the same fashion as described before.

Results.—A. Effect of Parenterally Administered Sulfanilamide on the Str. Viridans When Sulfanilamide Was Initially Introduced Within the Filter and Glass Capsules (concentration of 5 mg. per hundred cubic centimeters):

Inspection of table 4 indicates that the action of sulfanilamide was not nearly as effective as the action of sodium sulfapyridine on the growth of the three strains tested, although there appeared to be definite bacteriostasis in strain R and even partial sterilization in strain S. However, the growth of strain H appeared to be little affected by either the in vitro or the in vivo action of the sulfanilamide. It will be noted that in some capsules the concentration of sulfanilamide after twenty-four hours was high, indicating the ready transfer of parenterally administered sulfanilamide from body fluids to the interior of the capsule.

B. Effect of Parenterally Administered Sulfanilamide on Str. Viridans When Sulfanilamide Was Initially Introduced Within the Filter and Glass Capsules (concentration of 10 mg. per hundred cubic centimeters):

As shown again in table 4, the action of sulfanilamide on these three strains of streptococci was much less effective than that of sulfapyridine, but there seems to be no doubt that at this concentration there was definite bacteriostasis in all three strains and that there appeared to be a limited amount of sterilization in strains R and S. It should be observed that the in vivo action of sulfanilamide, acting alone, was no more effective than the in vitro action under the conditions of our experiments.

IV. EFFECT OF SODIUM SULFAPYRIDINE ON A FIBRIN-PLATELET MASS INFECTED WITH STR. VIRIDANS

The preceding experiments indicated that the parenteral administration of either sulfanilamide or sulfapyridine had a bacteriostatic effect on the three strains of Str. viridans studied, although the action of sodium sulfapyridine appeared to be more effective, for there was not only marked bacteriostasis when it was given but partial and complete sterilization in some of the experiments with these three strains. However, it was seen that to effect bacteriostasis and sterilization by the administration of sodium sulfapyridine, and presumably also of sulfanilamide, it was necessary to reach an effective concentration of the drug within the capsule before the bacteria were too far advanced in their growth. To study this last point further, it was decided to introduce fibrin-infected masses, suspended in sterile dog's serum in the same type of filter capsules previously utilized, and after peritoneal implantation of these filter capsules to treat the rabbits daily with sodium sulfapyridine

TABLE 4.—*Effect of the Parenteral Administration of Sulfanilamide on the Growth of Str. Viridans with Introduction of Sulfanilamide into Capsules before Peritoneal Implantation*

Rabbit	Type of Container Introduced	Initial Sodium Sulfanilamide in Container, Mg. per 100 Cc.	Total Parenteral Administration of Sulfanilamide, Gm.	Sulfanilamide in Container After 24 Hours, Mg. per 100 Cc.	Initial Number of Streptococci Added to Container	Number of Streptococci in Container After 24 Hours	Temperature (C.) of Rabbit 8 Hours After Operation	Growth of Container Fluid on Blood Agar	Duration of Experiment, Hours
				Strain H					
1	Filter capsules Ia	5	4.8	15.0	1.0×10^8	1.1×10^{11}	39.2	++++	24
	Filter capsules IIa	5	4.8	15.8	1.0×10^8	2.8×10^{11}	39.2	++++	24
2	Filter capsules Ib	5	4.8	9.2	1.0×10^8	7.5×10^{10}	39.6	++++	24
	Filter capsules IIb	5	4.8	10.0	1.0×10^8	1.0×10^{11}	39.6	++++	24
3	Glass containers Ic	5	0	5.0	1.0×10^8	3.0×10^{11}	39.0	++++	24
	Glass containers IIc	5	0	5.0	1.0×10^8	2.5×10^{11}	39.0	++++	24
4	Filter capsules Id	10	4.8	12.5	1.0×10^8	4×10^9	39.6	++++	24
	Filter capsules IId	10	4.8	11.8	1.0×10^8	1.2×10^{10}	39.6	++++	24
5	Filter capsules Ie	10	3.0	8.5	1.0×10^8	3.0×10^9	40.0	++++	8
	Filter capsules IIe	10	3.0	7.7	1.0×10^8	7.0×10^9	40.0	++++	8
6	Glass containers If	10	0	10.0	1.0×10^8	1.7×10^{10}	39.6	++++	24
	Glass containers IIf	10	0	10.0	1.0×10^8	2.0×10^{10}	39.6	++++	24
7	Filter capsules Ig (control)	0	0	0	1.0×10^8	9.0×10^{11}	39.2	++++	24
	Filter capsules IIg (control)	0	0	0	1.0×10^8	7.5×10^{11}	39.2	++++	24
				Strain R					
8	Filter capsules Ia	5	5.4	12.5	1.5×10^8	4.5×10^7	39.2	++++	24
	Filter capsules IIa	5	5.4	15.0	1.5×10^8	3.0×10^7	39.2	++++	24
9	Filter capsules Ib	5	5.4	10.2	1.5×10^8	1.0×10^8	39.4	++++	24
	Filter capsules IIb	5	5.4	12.4	1.5×10^8	5.4×10^7	39.4	++++	24
10	Glass containers Ic	5	0	5.0	1.5×10^8	7.5×10^7	39.0	++++	24
	Glass containers IIc	5	0	4.8	1.5×10^8	6.0×10^7	39.0	++++	24
11	Filter capsules Id	10	5.4	12.5	1.5×10^8	1.0×10^7	38.8	++++	24
	Filter capsules IId	10	5.4	14.0	1.5×10^8	2.0×10^7	38.8	++++	24
12	Filter capsules Ie	10	5.4	15.2	1.5×10^8	2.0×10^7	39.0	++++	24
	Filter capsules IIe	10	5.4	14.0	1.0×10^8	3.6×10^7	39.0	++++	24
13	Glass containers If	10	0	10.0	1.5×10^8	2.4×10^7	39.2	++++	24
	Glass containers IIf	10	0	9.8	1.5×10^8	2.8×10^7	39.2	++++	24
14	Filter capsules Ig (control)	0	0	0	1.5×10^8	8.7×10^{11}	39.0	++++	24
	Filter capsules IIg (control)	0	0	0	1.5×10^8	9.4×10^{11}	39.0	++++	24
				Strain S					
15	Filter capsules Ia	5	1.6	6.3	5.5×10^7	7.5×10^4	....	++++	8
	Filter capsules IIa	5	1.6	4.3	5.5×10^7	6.5×10^4	....	+++	8
16	Filter capsules Ib	5	3.2	3.3	5.5×10^7	8.0×10^4	39.2	+++	24
	Filter capsules IIb	5	3.2	4.0	5.5×10^7	6.0×10^4	39.2	+++	24
17	Glass containers Ic	5	0	5.3	5.5×10^7	9.0×10^4	39.8	+++	24
	Glass containers IIc	5	0	5.1	5.5×10^7	7.5×10^4	39.8	+++	24
18	Filter capsules Id	10	7.2	15.2	5.5×10^7	4.0×10^3	38.8	++	24
	Filter capsules IId	10	7.2	12.4	5.5×10^7	8.0×10^3	38.8	+++	24
19	Filter capsules Ie	10	7.2	16.0	5.5×10^7	1.5×10^4	39.4	+++	24
	Filter capsules IIe	10	7.2	12.0	5.5×10^7	6.7×10^3	39.4	++	24
20	Glass containers If	10	0	9.0	5.5×10^7	$<5 \times 10^3$ *	38.8	+	24
	Glass containers IIf	10	0	9.0	5.5×10^7	5.0×10^3	38.8	+	24
21	Filter capsules Ig (control)	0	0	0	5.5×10^7	3.9×10^{11}	39.2	++++	24
	Filter capsules IIg (control)	0	0	0	5.5×10^7	5.4×10^{11}	39.2	++++	24

* Dilutions for counting were begun at this level.

and at intervals of days to open the abdomen and determine whether sterilization had occurred. In this manner, it was believed, a stimulation of the clinical disease process would be obtained, for this fibrin focus in the filter capsule would be isolated from living tissue, either fixed or circulating, and could be reached only by the fluids of the body, just as has been demonstrated is the condition in the vegetation of streptococcic origin situated on a heart valve.

TABLE 5.—*Effect of Prolonged Parenteral Administration of Sulfanilamide and Sodium Sulfapyridine on the Persistence of a Focus of Infection by Str. Viridans*

Rabbit	Type of Container Introduced Within Rabbit	Strain of Organism	Daily Administration of Drug, Gm.	Total Amount of Drug Given, Gm.	Duration of Experiment, Days	Viable Str. Viridans Present in Capsule?	Final Concentration of Drug in Capsule, Mg. per 100 Cc.
			Sulfanilamide				
1	Filter capsules Ia	R	1.5	7.5	5	Yes	10.5
	Filter capsules IIa	R	1.5	7.5	5	Yes	9.0
2	Filter capsules Ib	R	1.5	9.0	6	Yes	4.0
	Filter capsules IIb	R	1.5	9.0	6	Yes	5.0
3	Filter capsules Ic	S	0.75	10.95	15	Yes	3.0
	Filter capsules IIc	S	0.75	10.95	15	Yes	6.0
			Sulfapyridine				
4	Filter capsules Ia	R	1.5	7.5	5	Yes	5.0
	Filter capsules IIa	R	1.5	7.5	5	Yes	6.0
5	Filter capsules Ib	R	1.5	9.0	6	Yes	4.0
	Filter capsules IIb	R	1.5	9.0	6	Yes	5.0
6	Filter capsules Ic	S	1.0	14.85	15	Yes	1.2
	Filter capsules IIc	S	1.0	14.85	15	Yes	3.0
			Control				
7	Filter capsules Ia	R	0	0	6	Yes	0
	Filter capsules IIa	R	0	0	6	Yes	0
8	Filter capsules Ib	S	0	0	15	Yes	0
	Filter capsules IIb	S	0	0	15	Yes	0

Method.—Into six of ten filter capsules were placed five fibrin-platelet masses, about 5 mm. in diameter, which had been previously suspended for twenty-four hours in a dextrose broth culture of strain R organisms; then sterile dog's serum was added to fill the capsules completely. The remaining four filter capsules were treated in the same manner except that the fibrin masses introduced into their cavities were previously impregnated with strain S organisms.

After all capsules were capped with rubber and sealed with sterile paraffin, they were introduced into the peritoneal cavities of 5 rabbits; thus, 3 rabbits received two capsules each containing the fibrin-platelet masses impregnated with the strain R organisms, and 2 rabbits received two capsules each containing the fibrin-platelet masses impregnated with the strain S organisms. Then sodium sulfapyridine was administered parenterally (by intravenous and intraperitoneal injection) three times a day to 3 of these rabbits until the end of the experiment. The capsules in the 2 remaining rabbits, which were not treated, one capsule containing strain

R and the other containing strain S organisms, were used as controls. At the end of the experiment, the rabbits were operated on again, the capsules were removed under aseptic conditions, blood agar plates were directly inoculated with their contents and a determination of the sodium sulfapyridine content was made.

Results.—As table 5 clearly demonstrates, in none of the animals receiving sulfapyridine were the contents of the filter capsules sterile when examined at the end of the experiment, although in 1 animal the capsules remained in the peritoneal cavity for fifteen days and this animal received a total of 14.85 Gm. of sodium sulfapyridine. It will be observed, too, that all capsules contained significant amounts of sodium sulfapyridine, indicating that there was a transfer of sodium sulfapyridine from the body fluids to the interior of the capsules. In the light of these observations, it must be concluded that the administration of relatively large amounts of sodium sulfapyridine will not sterilize a focus of infection caused by Str. viridans within the body of a rabbit if this focus is shielded from living tissue, even though sodium sulfapyridine therapy may be continued for as long as fifteen days.

V. EFFECT OF SULFANILAMIDE ON A FIBRIN-PLATELET MASS INFECTED WITH STR. VIRIDANS

Although the relatively poor bacteriostatic effect of parenterally administered sulfanilamide on a small inoculum of Str. viridans not protected by fibrin offered almost no hope that prolonged administration of the drug would be more effective in the sterilization of a fibrin-platelet mass impregnated with Str. viridans, it was thought nevertheless advisable to determine actually the efficacy of this type of extended treatment.

Method.—Exactly the same procedure as described under "Method" in section IV was carried out, except that sulfanilamide in 0.8 per cent solution was given parenterally (by intravenous and intraperitoneal injection).

Results.—All capsules when examined (table 5), whether they had remained in the peritoneal cavity for five, six or fifteen days, revealed the persistence of Str. viridans. Also, determination of the capsular concentration of sulfanilamide demonstrated conclusively that sulfanilamide readily entered the capsule during the experiment. Again, as was found with the more potent sodium sulfapyridine, the effectiveness of parenterally administered sulfanilamide in sterilizing a focus of infection caused by Str. viridans, closely similar to an actual vegetation from a functional standpoint, was almost nil.

VI. EFFECT OF SULFANILAMIDE AND SULFAPYRIDINE IN THE TREATMENT OF CLINICAL SUBACUTE ENDOCARDITIS

The results already described concerning the effectiveness of sulfapyridine and sulfanilamide on Str. viridans in relation to subacute endocarditis uniformly pointed to the fact that from an experimental viewpoint these drugs appear to be unable to eradicate a focus of streptococci growing in and protected by a fibrin-platelet mass. However, it would be foolhardy to suggest the complete elimination of the use of these drugs in the treatment of subacute endocarditis if there were some remote

possibility that they could effect clinical results, despite their seeming ineffectiveness on a focus of Str. viridans under controlled laboratory conditions. Accordingly, a study of the cases of 12 patients treated with these drugs was made and the results analyzed. It is important

TABLE 6.—*Data on Twelve Clinical Cases of Subacute Endocarditis Treated with Sulfapyridine and Sulfanilamide*

Case Number	Patient	Age, Years	Duration of Illness Before Treatment, Months	Dose per Day, Gm.	Duration of Therapy, Days	Additional Therapy	Final Result
				Sulfapyridine			
1	W. R.	60	2.5	5	105	Heparin, 35 days	Death*
2	N. V.	7½	2	4	6	Heparin, 21 days	Death
3	K. J.	20	5	3	10	Supportive measures	Death
4	G. M.	25	2	5.5	60	Supportive measures	Death
5	W. N.	23	2.5	4	15	Supportive measures	Death
6	A. P.	32	5	4	8	Supportive measures	Death*
				Sulfanilamide			
7	S. B.	34	1.5	5	42	Heparin, 14 days	Death*
8	I. G.	61	0.5	2.5	21	Supportive measures	Death
9	H. K.	52	2	5	30	Supportive measures	Death*
10	S. G.	46	1	4 to 8	40	Cacodylate	Death
				Sulfanilamide and Sulfapyridine			
11	G. P.	34	1.5	6 Gm. of sulfanilamide for 6 days and 2 Gm. of sulfapyridine for 8 days	14	Supportive measures	Death
12	C. S.	24	3.5	4 Gm. of sulfanilamide for 4 days and 3 Gm. of sulfapyridine for 5 days	9	Supportive measures	Death

* Autopsy was performed.

to point out that these cases were not selected from one institution but were collected from five different hospitals and represent the last successive cases of this disease in three of these five institutions.

Each of the 12 patients studied exhibited a cardiac murmur or murmurs, splenomegaly, a minimum of two blood cultures positive for Str. viridans, fever, progressive anemia and loss of weight. Ten of the patients also presented petechiae; 10 of them had red blood cells in their urine, and 5 had clinical evidences of embolus. In none of these

cases, with the exception of 1, was there any clinical doubt of the diagnosis, and in this 1 case the only doubt was whether rheumatic fever also was not present.

As table 6 indicates, 6 of the 12 patients received sulfapyridine alone for a period varying from six to one hundred and five days, and in all 6 the results have been worthless. Two of these patients also received heparin in conjunction with the sulfapyridine. Patient W. R. (table 6) received 3 to 4 ampules of purified heparin a day for thirty-five days, together with 5 Gm. of sulfapyridine over the same period. Patient N. V. (table 6) was given heparin with neoarsphenamine for twenty-one days, after a trial with sulfapyridine resulted in no improvement. In both of these patients, despite the maintenance of a prolonged coagulation time (fifteen to thirty minutes) for a period of five and three weeks, respectively, there was no noticeable improvement and the blood cultures continued to be positive. In the 2 patients just mentioned, the occurrence of a thrombus in the vein just beyond the needle through which the heparin was passing into the vein led us to believe that thrombus deposits may have continued on the vegetation despite the intensive heparin therapy.

Those 4 patients who received sulfanilamide alone fared no better, as table 6 shows, even though the therapy was of fairly long duration, averaging thirty-one days. It is of interest to point out that the blood cultures of these 4 patients continued positive for Str. viridans, even those of S. B., who also received heparin for fourteen days.

The 2 patients who received sulfanilamide and later sulfapyridine also died, although it is obvious that in neither case was the therapy extensive either in quantity of drugs given or in duration.

Thus, of these 12 patients, all have died. It would seem, then, that the effect of either of these drugs on Str. viridans present in a cardiac vegetation is no more effective than that observed on the same organism under controlled experimental conditions.

COMMENT

The inability of either sulfanilamide or sulfapyridine to penetrate easily a fibrin-platelet mass containing Str. viridans is of course discouraging, for these two drugs are ordinarily considered to be fairly diffusible and if they can penetrate the mass but slowly, it would seem that the chances for any new chemical substance to penetrate more readily will also be slight. Again, it must be emphasized that any drug used in the treatment of subacute endocarditis must be able to penetrate a fibrin-platelet mass if it is to be effective.

The production of a focus of protected growth of Str. viridans in the abdomen of the rabbit with the concomitant parenteral administration

of sulfapyridine or sulfanilamide to the same animal gave interesting results. They indicated clearly that both of these drugs were no more effective against Str. viridans in vivo than they were in vitro, but if the inoculum was small and if its growth had not been allowed to progress too far, the effectiveness of either drug, in particular that of sulfapyridine, was so marked that it was unnecessary to suppose that living tissue would have aided further in the destruction of the organism. It may well be that the powerful effect of these drugs when given parenterally to animals infected with the hemolytic streptococcus, as contrasted with their possible equivocal action on the same organism in the test tube, is due to the fact that the bacterial invasion in the body is relatively slight and the number of bacteria per unit of invaded tissue is small and far less than the average number of bacteria present in various test tube experiments concerned with the determination of the germicidal activity of these drugs.

Despite the remarkable effectiveness of sulfapyridine and the lesser effect of sulfanilamide on Str. viridans when these drugs were placed in immediate contact with a small inoculum, it was found that if there was as little as six hours' delay in the contact between either of the drugs and the initial inoculum of Str. viridans the bactericidal action of either drug, despite the concentrations finally obtained, was nil. Then, too, the experimental production of a fibrin-platelet mass infected with this same organism but separated from living tissue by means of a procelain filter capsule led to a persistence of infection despite the quantity and duration of administration of either drug. It was thought that this last procedure was a simulation of the disease process present in the patient suffering from subacute endocarditis.

Finally, a study was made of the cases of 12 patients with subacute endocarditis caused by Str. viridans who were treated with sulfanilamide or sulfapyridine or both, and in every case the effectiveness of these drugs was found to be negligible. Patients in 3 of these cases received intensive heparin therapy in conjunction with sulfapyridine or sulfanilamide, and the results were equally negative. Although one of us (M. F.) and his associates [18] were the first to suggest and use heparin in the treatment of subacute endocarditis and although favorable results have been reported by Kelson and White,[14] it is now believed by us that its action either alone or with sulfapyridine is of no real value in the treatment of this disease.

18. Friedman, M.; Hamburger, W. W., and Katz, L. N.: Use of Heparin in Subacute Bacterial Endocarditis: A Preliminary Report, J. A. M. A. **113**:1702 (Nov. 4) 1939.

SUMMARY

The permeability of a fibrin-platelet mass to sulfanilamide and sulfapyridine was studied and was found to be limited.

The in vivo action of sulfanilamide and sulfapyridine on Str. viridans was studied by means of a new technic, and the results were compared with those from the in vitro action of the drugs. It was found that the in vivo and the in vitro activity of these two drugs were apparently identical.

The production of a focus of infection by Str. viridans in the rabbit functionally similar to the focus of infection found in the patient suffering with subacute endocarditis was accomplished, and it was found that the administration of either sulfanilamide or sulfapyridine did not result in the sterilization of this focus, despite a substantial duration of therapy.

A series of 12 clinical cases of subacute endocarditis treated with sulfapyridine and sulfanilamide is reported. The patients in 3 of these cases also received heparin therapy. The effect of sulfanilamide or sulfapyridine was found to be negligible. The concomitant use of heparin in the treatment of 2 patients receiving sulfapyridine and of 1 patient receiving sulfanilamide did not increase the effectiveness of either drug in combating the infection.

The sodium sulfapyridine and sulfanilamide used in these experiments were given to us by the Abbott Laboratories, North Chicago.

Drs. W. S. Middleton and P. F. Clark, of the University of Wisconsin, gave aid and encouragement in the experimental and clinical phases of this study. Drs. L. Briggs, B. Kaufman and J. M. Rector, of San Francisco, and Dr. L. N. Katz, of Chicago, allowed us the use of their clinical protocols for this study. Miss M. Hooper gave technical assistance in the execution of this problem.

A CORRELATION OF THE VELOCITY OF BLOOD FLOW AND THE BASAL METABOLIC RATE

SAMUEL BAER, M.D.
Associate in Medicine, the Jewish Hospital
AND
HAROLD J. ISARD, M.D.*
Lieutenant, Medical Corps, United States Marines
PHILADELPHIA

It is more than a hundred years since Parry,[1] Graves [2] and Basedow [3] first accurately described hyperthyroidism and called attention to some of the cardiovascular derangements present in this condition, but it was not until twenty-five years ago that clinical calorimetry began to be widely adopted as an aid in the diagnosis of exophthalmic goiter. Today the determination of the basal metabolic rate is the laboratory procedure most frequently used in the differential diagnosis of disorders of the thyroid gland.

Disturbances of the thyroid gland, however, are not the only conditions producing changes in the basal metabolic rate. The basal metabolic rate is elevated not only in hyperthyroidism, but also in leukemia, congestive heart failure, some cases of hypertension, fevers, polycythemia vera and various glandular disturbances. Furthermore, hypopituitarism and malnutrition as well as hypothyroidism may lower the basal metabolic rate. For these reasons attempts have been made to find procedures other than the determination of the basal metabolic rate that might be of help in the differential diagnosis of these disorders.

During the past decade increasing interest has also been manifested in the estimation of the velocity of blood flow. Blumgart and his asso-

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From the wards and outpatient departments, Jewish Hospital.

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* At the time this work was done Dr. Isard was an assistant in the Metabolic Department, the Jewish Hospital.

1. Parry, C. H.: Collections from the Medical Writings of the Late Caleb Hillier Parry, London, Underwood, 1825, vol. 1, p. 478.

2. Graves, R. J.: Newly Observed Affection of the Thyroid Gland in Females, London M. & S. J. **7**:516, 1835.

3. Basedow, C. A.: Exophthalmos durch Hypertrophie des Zellgewebes in der Augenhöhle, Wchnschr. f. d. ges. Heilk. **6**:197 and 220, 1840.

ciates [4] first described the method using radium C for measuring the speed of the circulating blood. They [4c] demonstrated that myxedema and thyrotoxicosis were accompanied by changes in the rate of pulmonary blood flow. Later Tarr, Oppenheimer and Sager,[5] determining the circulation time by the decholin method, also reported an increased velocity of blood flow in hyperthyroidism and a slowing in myxedema. Others [6] have confirmed their work. However, some of the data we obtained in studying circulation times seemed contrary to previously published results. We decided, therefore, to reinvestigate the subject and determine what correlation, if any, existed between the basal metabolic rate and the velocity of blood flow.

METHOD

The studies were performed on patients in the wards and outpatient departments of the Jewish Hospital. All circulation times were measured by us, and over 90 per cent of the determinations of the basal metabolic rate were done by the same technician.

The subjects for the study (if ambulant) were put to bed and made to lie quietly for one-half to one hour. With the patient satisfactorily at ease, the basal metabolic rate was then determined by means of the Jones or Sanborn machine. The test was considered satisfactory only if smooth, regular graphs were obtained. During the same morning, under basal conditions, circulation times were determined.

The circulation time (arm to tongue) of calcium gluconate [7] was determined as described by Goldberg [6b] and then by Baer and Slipakoff.[8] By means of an 18 gage needle and a 10 cc. syringe containing 8 cc. of a 20 per cent solution of calcium gluconate, 4 cc. was injected into an antecubital vein. The intravenous injection of a 20 per cent solution of calcium gluconate causes a sudden sensation of heat in the tongue and pharynx, which rapidly spreads to the face, perineum and extremities. We modified Goldberg's procedure by using 4.0 cc. rather than the originally suggested 2.5 cc. for each test. The greater quantity

4. (*a*) Blumgart, H., and Yens, O. C.: Studies on Velocity of Blood Flow, J. Clin. Investigation **4**:1, 1927. (*b*) Blumgart, H., and Weiss, S.: Velocity of Blood Flow in Normal Individuals, ibid. **4**:16, 1927. (*c*) Blumgart, H.; Gargill, S., and Gilligan, D. R.: Velocity of Blood Flow in Myxedema and Thyrotoxicosis, ibid. **9**:91, 1930. (*d*) Blumgart, H.: Velocity of Blood Flow in Health and Disease, Medicine **10**:1, 1931.

5. Tarr, L.; Oppenheimer, B. S., and Sager, R. V.: Circulation Time Determined by Use of Sodium Dehydrocholate, Am. Heart J. **8**:766, 1933.

6. (*a*) Macy, J. W.; Claiborne, T. S., and Hurxthal, L. M.: Circulation Time in Relation to Metabolism in Thyroid and Pituitary States (Decholin Method), J. Clin. Investigation **15**:37, 1936. (*b*) Goldberg, S. J.: Use of Calcium Gluconate as a Circulation Time Test, Am. J. M. Sc. **192**:36, 1936; (*c*) Circulation Time as a Diagnostic Aid in Hyperthyroidism, Ann. Int. Med. **11**:1818, 1939.

7. Calcium gluconate, in the form of calcium gluconogalactogluconate, in a 20 per cent solution, was supplied by the Sandoz Chemical Works, Inc., New York.

8. Baer, S., and Slipakoff, B. G.: Measurement of Circulation Times and the Agents Used in Their Determination, Am. Heart J. **16**:29, 1938.

gave a more intense reaction. The injection was timed from the moment it was begun until the instant the sensation of heat was felt in the throat. Duplicate readings were usually made with the remainder of the 8 cc.

With the same needle in situ, the circulation time (arm to lung) of ether (Hitzig [9]) was determined. A mixture of 5 minims (0.3 cc.) of ether and 5 minims of physiologic solution of sodium chloride was injected intravenously; the end point was the perception in the patient's breath of ether vapor, which was readily recognized by the observer and frequently caused the patient to cough or grimace.

All circulation rates were recorded in seconds and timed by a stop watch from the beginning of the injection to the instant the end point was recognized.

RESULTS

Circulation Time of Ether.—The circulation time (arm to lung) of ether was obtained in 250 determinations on 218 patients. Some of these results are summarized in table 1. One of us (Dr. Baer) and an associate [8] previously confirmed the observations by Hitzig [9] and Oppenheimer and Hitzig [10] that the normal circulation time of ether ranges

TABLE 1.—*Circulation Time of Ether (Arm to Lung)*

	Normal Health	Hyperthyroidism	Spontaneous Hypothyroidism	Postoperative Hypothyroidism
Number of patients	157	18	6	3
Number of determinations	178	23	6	3
Average time	5.5 sec.	4.6 sec.	7.0 sec.	6.5 sec.

from 3.5 to 8.0 seconds, with an average of 5.5 seconds. Four of the 250 determinations were outside the normal range. (The data on normal patients have not been presented in their entirety, but merely summarized.) In another paper [11] we showed that, with rare exceptions, the circulation time of ether falls within normal limits unless incipient or definite failure of the right side of the heart is present. There is nothing to contradict this statement in our studies here. The circulation time of ether, therefore, has little, if any, value in the study of metabolic disorders.

Circulation Time of Calcium Gluconate.—By means of the method using the calcium gluconate, 399 tests of circulation time were done on 187 patients. Goldberg [6b] and Baer and Slipakoff [8] showed that the

9. Hitzig, W. H.: Use of Ether in Measuring Circulation Time from the Antecubital Veins to the Pulmonary Arteries, Am. Heart J. **10**:1080, 1935.

10. Oppenheimer, B. S., and Hitzig, W. H.: Use of Circulatory Measurements in Evaluating Pulmonary and Cardiac Factors in Chronic Lung Disorders, Am. Heart J. **12**:257, 1936.

11. Baer, S., and Isard, H. J.: Use of Ether Circulation Time in the Diagnosis of Right Heart Failure, Am. J. M. Sc. **200**:209, 1940.

normal arm to tongue time obtained with a 20 per cent solution of calcium gluconate ranges from 9 to 16 seconds, with an average of 12.5 to 12.7 seconds. Performing the test with 4.0 cc. rather than the 2.5 cc. originally suggested by Goldberg,[6b] we found (table 2) in 227 trials that the average was 12.1 seconds; 10 of the 227 determinations were outside the normal range, and only 1 varied more than a second from the extremes of normal. Determinations of the metabolic rate were done in 119 instances on 110 normal patients. All but 19 were within the accepted normal range for the basal metabolic rate (+ 15 to — 15 per cent). In no adult patient clinically considered normal were both the basal metabolic rate and the circulation time outside the normal range.

Twenty-four patients with a clinical diagnosis of active hyperthyroidism were examined. The results are recorded in table 3. In this group the circulation time of calcium gluconate ranged from 7.0 to 13.2 seconds, with an average of 8.9 seconds. Tarr and his associates [5] obtained 9.0 seconds, and Goldberg,[6c] 8.8 seconds. Only 6 of the 46 determinations were above 10 seconds. Since a part of the basis for the diagnosis of hyperthyroidism was the basal metabolic rate, all but 1 of the patients had an elevated basal metabolic rate. This patient (case 280), with a basal metabolic rate of + 6 per cent and a definite thyroid adenoma, had been taking compound solution of iodine U. S. P. for months. Judged strictly, she could be eliminated from this group.

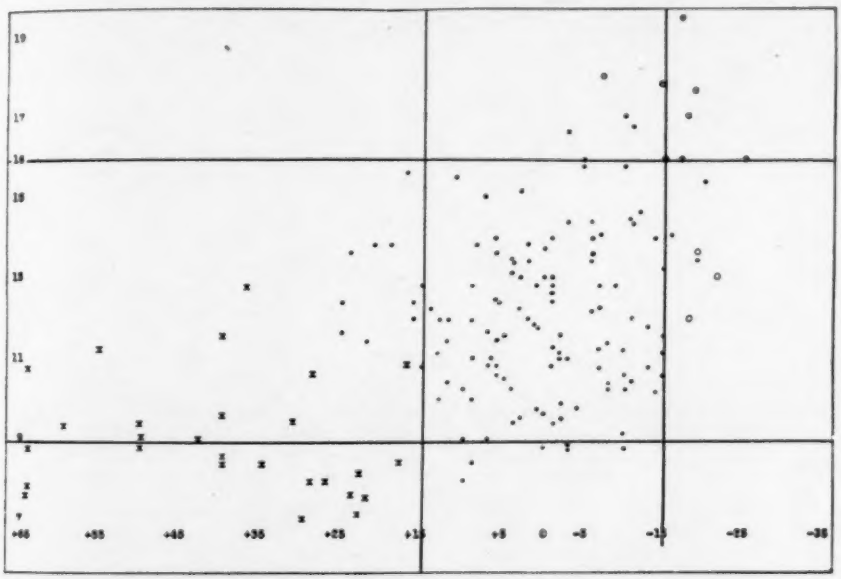
TABLE 2.—*Circulation Time of a 20 Per Cent Solution of Calcium Gluconate (Arm to Tongue)*

	Normal Health	Hyperthyroidism	Spontaneous Hypothyroidism	Postoperative Hypothyroidism	Menopause with Hypertension
Number of patients	110	24	6	3	18
Number of determinations	227	46	14	7	48
Average time	12.1 sec.	8.9 sec.	15.6 sec.	17.6 sec.	11.1 sec.

Table 4 lists the data on 9 patients with spontaneous and postoperative hypothyroidism. Of the 21 circulation times of calcium gluconate determined on these patients, 13 were prolonged to or beyond 16 seconds. The average circulation time for the patients with spontaneous hypothyroidism was 15.6 seconds and for those with postoperative hypothyroidism 17.6 seconds.

These results can be visualized more clearly on the graph, in which the circulation time is plotted against the basal metabolic rate. It would appear that though there is some overlapping of groups, an elevated

basal metabolic rate in hyperthyroidism is accompanied by a circulation time that is more rapid than normal or is in the low normal range. The patients with hypothyroidism, on the contrary, exhibit, in the majority of instances, a low basal metabolic rate and a circulation time above 13 seconds. In these patients there is some parallelism between the basal metabolic rate and the velocity of blood flow, as suggested by Blumgart, Gargill and Gilligan [4c] and others.[12] When conditions simulating thyroid disorders were considered, however, this relationship did not hold.



A graphic presentation of the relation between the circulation time and the basal metabolic rate in normal persons (solid dots), patients with hyperthyroidism (*x*) and patients with hypothyroidism (hollow circles). The basal metabolic rate is plotted as abscissas and the circulation time in seconds as ordinates.

Table 5 lists the data on 6 patients with polyglandular dystrophy. It is apparent that there was no correlation whatsoever between the velocity of blood flow and the basal metabolic rate. In case 181 the patient exhibited prolonged circulation times despite a consistently elevated basal metabolic rate, and in case 61, a rapid circulation time

Footnote 12 has been deleted.

13. (*a*) Webb, G.; Sheinfeld, W., and Cohn, H.: Importance in Surgery of Blood Circulation Time, Ann. Surg. **104**:460, 1936. (*b*) Fishberg, A. M.: Heart Failure, Philadelphia, Lea & Febiger, 1937, pp. 527-539. (*c*) Tarr, Oppenheimer and Sager.[5]

TABLE 3.—*Data on Patients with Active Hyperthyroidism*

Case Number	Sex	Age	Pulse Rate	Blood Pressure	Ether Time, Sec.	Calcium Gluconate Time, Sec.	Basal Metabolic Rate, per Cent
9	F	36	90	150/ 80	5.3	8.0 9.0	+63 +33 +65 +25 +53 +41
10	F	46	96	170/ 80	4.5	8.0 8.0	....
12	F	33	88	.....	...	7.4 8.2	+77 +100
29	F	62	80	175/100	5.0	9.2 10.0	+40
101	F	47	90	115/ 75	3.0	7.2 7.2	+30
114	F	28	86	.....	5.4	12.8	+45 +30
176	F	63	90	170/ 60	5.0	9.0 9.0	+43 +44
157	F	35	90	110/ 75	4.8 5.5	10.0 9.0 7.8 9.0	+51 +49 +35
195	F	44	80	160/100	4.0	7.1 8.0	+22
220	F	47	100	.....	4.0	7.2 8.0	+73
215	F	27	80	120/ 80	5.0	8.1 9.4	+18
270	F	45	100	120/ 70	5.2	8.6 9.5	+70 +60 +43 +59
277	M	40	100	120/ 75	5.1	8.6 9.0	+77 +60 +43 +59
278	M	40	80	110/ 75	...	8.0	+29
231	F	41	95	112/ 70	4.0	8.0 9.0	+55 +46 +21
177	F	61	75	140/ 90	5.9	10.9	+17
280	F	57	85	170/ 90	4.5	10.0	+6
244	F	39	86	82/ 64	4.6	8.2 13.0	+29
252	M	46	150	130/ 60	5.2	10.4 11.2	+70
263	F	56	68	140/ 70	...	9.9 13.2	+46 +34
257	F	28	75	.....	4.2	7.0 9.0	+27
274	M	26	90	140/ 80	...	9.1 9.8	+60
281	F	24	95	125/ 60	...	7.2 7.2	+19 +25
291	F	56	90	150/ 80	...	8.8 9.0	+45
Average.....					4.6	8.9	

TABLE 4.—*Data on Patients with Hypothyroidism*

Case Number	Sex	Age	Weight, Pounds	Pulse Rate	Blood Pressure	Ether Time, Sec.	Calcium Gluconate Time, Sec.	Basal Metabolic Rate, per Cent
				Spontaneous				
13	F	45	167¼	56	100/ 70	9.0	16.0	—25
21	F	50	151	66	110/ 80	8.0	12.0 13.0	—19 —18
50	F	46	114	52	120/ 18	7.2	16.0 12.6 13.2 16.0	—15 — 6 —17
81	F	38	157¼	44	.....	4.4	18.0 21.2	—17
129	F	14	133½	64	110/ 75	7.0	14.0 20.0 20.0	—15
269	F	46	212	64	120/ 84	6.4	13.4 14.0 13.0	—21 —19 —11 —21
Average						7.0	15.6	
				Postoperative				
60	M	60	144	55	200/120	8.0 7.6	18.0 17.0 17.0	—18 — 2
11	F	24	140	84	130/ 90	4.0	18.0 18.0	— 7 —16
278	F	51	159	72	170/100	...	16.2	—19
Average						6.5	17.6	

TABLE 5.—*Data on Patients with Polyglandular Dystrophies*

Case No.	Sex	Age	Weight, Pounds	Pulse Rate	Blood Pressure	Ether Time, Sec.	Calcium Gluconate Time, Sec.	Basal Metabolic Rate, per Cent	Comment
181	F	40	...	95	215/115	...	17.8 18.0	+25 +50 +31	Hypertension and dyspituitarism
212	M	51	155¼	54	98/ 60	8.4 6.4	14.4 12.0 14.8 20.0	—17 — 1	Hypopituitarism
87	F	40	242	80	155/100	8.0	9.5 11.6	+30 +11	Adrenal cell rest tumors of both ovaries
61	F	19	133½	80	120/ 70	5.4 5.0	7.2 9.8 8.0 7.8 10.4	— 4 —20	Pituitary dysfunction
225	F	30	215	78	125/ 95	4.4	10.0	+17	Possible basophilic adenoma of pituitary
36	M	18	251	72	.....	5.0 5.0 6.2	9.0 9.0 9.6 10.6 10.2 12.8	+19 —10 — 9	Dystrophic adiposogenitalis

and a low basal metabolic rate. Though these patients are few, we feel that they exhibit no relationship between the rapidity of blood flow and the metabolic rate.

TABLE 6.—*Data on Patients with Menopausal Syndrome and Hypertension*

Case Number	Age	Weight, Pounds	Pulse Rate	Blood Pressure	Ether Time, Sec.	Calcium Gluconate Time, Sec.		Basal Metabolic Rate, per Cent
1	46	135	76	180/100	5.6	9.6	11.6	+22
					4.0	10.4	12.2	− 1
					5.8	10.0		+10
						10.8		
4	59	152½	60	148/100	6.0	12.2		+21
						12.4		+ 5
						12.0		
						12.0		
20	50	150½	64	155/ 95	7.2	11.4		−11
						11.2		
22	50	185	55	165/105	7.2	12.8		+25
						14.0		− 8
						17.0		− 5
26	42	103	80	178/100	5.2	9.4		+20
						10.4		− 8
						10.4		+19
						8.8		− 3
34	49	166	82	195/ 95	5.0	8.8		− 8
						9.0		+15
						7.8		
66	54	132	70	150/100	4.0	9.1		+ 6
						12.1		
92	40	217	60	150/ 90	...	8.4		−14
						11.0		+22
						9.2		+23
						9.8		+25
105	48	147½	85	190/110	4.0	8.0		− 8
						8.8		
122	47	165	68	150/100	5.0	11.0		+ 5
						14.4		
139	50	169	66	140/100	7.4	10.4		+17
						11.4		
150	56	222	60	140/ 90	7.0	10.0		+ 9
						10.0		
163	42	195	72	130/ 90	4.8	10.4		+15
						11.4		
193	48	194½	62	180/ 90	8.0	11.2		+ 7
						11.4		
194	53	149	64	175/ 98	6.2	14.2		− 7
						13.4		
250	64	152	70	190/ 92	5.5	11.0		− 4
						11.2		
255	48	128¼	72	150/ 90	5.0	10.0		+ 4
						9.8		
272	37	131	88	130/ 90	6.2	9.8		+11
						10.0		
Average					5.7	11.1		

We further noticed during this study that a group of patients (table 6) with diverse clinical symptoms seemed to compose a definite class irrespective of the basal metabolic rates. These patients all had hypertension and were usually obese and in the menopausal period. King

and Sohval [14] considered the value of the basal metabolic rate and the velocity of blood flow in the differential diagnosis of hyperthyroidism. Of their 87 cases, autonomic imbalance, menopausal syndrome, hypertension or nontoxic goiter was present in 70. In these borderline states neither the basal metabolic rate nor the circulation time was diagnostic;

TABLE 7.—*Data on Children*

Case Number	Sex	Age	Weight, Pounds	Pulse Rate	Blood Pressure	Ether Time, Sec.	Calcium Gluconate Time, Sec.	Basal Metabolic Rate, per Cent
48	F	11	126	88	.....	4.0 4.6	9.2 10.2 7.3 8.9	—20 —21 —14
253	M	9	60	75	.....	...	8.0 7.8 8.0 10.1	+20 +19
15	F	13	145	70	110/ 70	7.0	11.5 11.0	—19
73	M	13	125	60	110/ 75	4.0	8.8 11.2	— 8
185	F	11	72½	80	.....	7.0	9.6 12.6	+11
202	M	10	100¼	72	.....	4.2	7.2 9.6	+ 1
209	F	14	145½	62	115/ 75	5.0	9.2 9.8	— 6
222	F	13	136	80	.....	3.4	4.5 7.4 5.6	—16
224	F	16	133½	68	115/ 90	3.6	6.4 8.0	+ 6
227	F	16	188	68	126/ 88	4.4	8.4 8.2	+ 9
260	F	12	...	74	.....	2.4	8.0 8.2	— 1
52	F	15	108	76	100/ 60	5.8	11.0	—21
64	F	8	49	110	110/ 70	2.8	5.3 6.2	+12
70	F	9	95¼	80	.....	4.0	7.2 6.0	+13 +20
160	F	10	77¼	80	.....	4.0	10.4	+11
241	M	11	113¾	68	.....	7.2	8.2 12.0	+ 2
Average.....						4.6	8.6	

the clinical judgment surpassed both laboratory studies in diagnostic accuracy. In the group of 18 patients we studied, circulation times ranged from 7.8 to 17.0 seconds, with an average of 11.1 seconds. Seven of the 50 measurements were outside the normal range of 9.0 to 16.0 seconds. Yet the basal metabolic rate varied from — 14 to + 25 per

14. King, F. H., and Sohval, A. R.: Value of Basal Metabolic Rate, Velocity of Blood Flow and Creatinine Tolerance Test in Differential Diagnosis of Graves' Disease, Ann. Int. Med. **13**:261, 1939.

cent and in 9 of 30 estimations was above + 15 per cent. In addition, repeated determinations of the basal metabolic rate showed a much greater variation than did the circulation times (cases 1, 4, 26, 34 and 92). The variations and overlapping in this group were such that we felt there was no definite relationship between the basal metabolic rate and the circulation time.

In table 7 are included data on 16 children on whom the basal metabolic rate and the velocity of blood flow were determined. Averbuck and Friedman [15] found the circulation time in children varied from 5.0 to 13.5 seconds, with an average of 8.6 seconds. The 35 determinations listed confirm their findings, our average also being 8.6 seconds. But it is seen that despite the consistently rapid circulation time in children, the basal metabolic rate varied from — 21 to + 20 per cent, and bore no relationship whatsoever to the circulation time. Further study is necessary to determine whether the shorter pathway due to the physical measurement of the child is a prime factor in production of these rapid rates.

COMMENT

Blumgart and his associates [4c] first pointed out that there was a relation between the velocity of blood flow, the pulse rate and the basal metabolic rate. Others [16] confirmed their observations, reporting a strikingly increased velocity of blood flow in cases of hyperthyroidism. Our study bears this out, but we cannot agree with Blumgart and his associates [4c] that the circulation time parallels the basal metabolic rate and that a given percentage of increase or decrease in the basal metabolic rate is accompanied by a far greater percentage of change in the velocity of blood flow. We did not, for example, observe consistently increased circulation times in cases of hypertension with an elevated basal metabolic rate. Macy and his co-workers,[6a] in studying the circulation rate in relation to metabolism, concluded there was no obvious circulatory change associated with hypometabolism which was not primarily thyroid in origin.

It would appear, then, that the basal metabolic rate itself is not the important factor influencing the velocity of blood flow in disturbances of the thyroid gland. Perhaps, as suggested by Fishberg,[13b] it is the effect of the amount of circulating thyroxin on the metabolism of the heart muscle itself that plays a predominant role in the circulatory adjustments to hyperthyroidism and hypothyroidism.

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15. Averbuck, S. H., and Friedman, W.: Circulation Time in Normal Children, Am. J. Dis. Child. **49**:361 (Feb.) 1935.

16. Tarr, Oppenheimer and Sager.[5] Macy, Claiborne and Hurxthal.[6a] Goldberg.[6c] Webb, Sheinfeld and Cohn.[13a] Fishberg.[13b]

It must be realized that the circulation time may not always be diagnostic of hyperthyroidism, any more than is the basal metabolic rate. There is too much overlapping to make the measurement of the velocity of blood flow an absolutely diagnostic procedure. The final diagnosis in borderline cases may depend entirely on clinical judgment, as suggested by King and Sohval.[14] They expressed the belief that the determination of the circulation time failed to give laboratory assistance in the differential diagnosis of exophthalmic goiter and the borderline states. We do believe, however, that it is of some definite value. Ninety per cent of the 46 determinations of the circulation time of calcium gluconate in patients with hyperthyroidism were 10 seconds or below. Of the normal group, only 22 per cent were 10 seconds or less, and of those patients exhibiting menopausal symptoms and hypertension, 39 per cent had circulation times of 10 seconds or below. An elevation of the basal metabolic rate above 20 per cent and a circulation time (arm to tongue) of calcium gluconate of 10.0 seconds or less, in our opinion, are strongly suggestive of active hyperthyroidism.

SUMMARY AND CONCLUSIONS

The circulation time of ether was determined in 218 patients. The circulation time of ether is of no value in the study of metabolic disorders.

The circulation of calcium gluconate was measured in 227 determinations on 110 normal patients and averaged 12.1 seconds.

In patients with hyperthyroidism or hypothyroidism, the circulation time roughly paralleled the basal metabolic rate. The circulation time is rapid in hyperthyroidism and slowed in hypothyroidism.

There is no correlation between the circulation time of calcium gluconate and the basal metabolic rate in polyglandular dystrophies or menopausal syndromes with hypertension. Irrespective of the basal metabolic rate, the circulation time is rapid in children.

The determination of the velocity of blood flow may be of some help in the diagnosis of derangement of the thyroid gland.

Dr. Harold L. Goldburgh and Dr. Leon Jonas gave us permission to undertake this study and offered advice and criticism.

OSTEOGENESIS IMPERFECTA

ITS INCIDENCE AND MANIFESTATIONS IN SEVEN FAMILIES

F. REGIS RIESENMAN, M.D.
AND
WALLACE M. YATER, M.D.
WASHINGTON, D. C.

Thirty-two members of 7 white families having osteogenesis imperfecta have been found to reside in or near Washington, D. C.[1] In 5 of the families there is a definite hereditary tendency, while in the other 2 families with no such tendency the disease is represented in its isolated form. The ascendants, descendants and collaterals of the various families were studied, and 91 cases of the disease were found in a total of 255 members. Seven generations of 1 family, six generations of 2 families and five generations of another family were traced. The origin of the condition in 1 of the family groups was in Ireland, in 1790; in 2 family groups, in Germany, 1 in 1735 and the other in 1770, and the remaining 4, in this country, 2 in Virginia, dating back to 1808 and 1896, and the other 2 in the District of Columbia.

HISTORICAL DATA

Osteogenesis imperfecta, otherwise called fragilitas ossium, has been recognized for more than one hundred and fifty years and blue sclerotics for more than a hundred years, but as unrelated conditions. The fragility factor was described by Ekman[2] in 1788, and the blue sclerotics were first recognized by Henzschel[3] in 1831. The fact that the two conditions occur in the same families and frequently in the same patients and that they are inherited abnormalities was definitely established by Spurway in 1896 and by Eddowes in 1900.[4] The first definite descrip-

From the Department of Medicine, Georgetown University School of Medicine.

1. The cases of only 8 of the 32 will be described in detail as illustrative material.

2. Ekman, O. J.: Descriptio et casus aliquot osteomalaciae, Upsala, J. Edman, 1788.

3. Henzschel, G.: Voräufige Notiz über den Irismangel bei drei Geschwistern, Ztschr. f. d. Ophth. **1**:52, 1831.

4. Spurway, J.: Hereditary Tendency to Fracture, Brit. M. J. **2**:844, 1896. Eddowes, A.: Blue Sclerotics and Fragile Bones, ibid. **2**:222, 1900; cited by Rodger, T. R.: Otosclerosis Associated with Blue Sclerotics and Fragilitas Ossium, Proc. Roy. Soc. Med. **29**:1107 (July) 1936.

tion of the disease was given by Lobstein, cited by Levent,[5] in 1833, and his name is often given to this syndrome. In 1916, van der Hoeve and de Kleijn[6] demonstrated before the Gröningen Medical Society the association of deafness with abnormal coloration of the scleras and fragility of the bones. They subsequently described the syndrome which bears their names and which appears to be a particular and more complete form of the disease. The syndrome is not always complete; one, or even two, of the symptoms in the triad may not be present. The most common member of the symptomatic triad is the ocular abnormality in which the scleras present "a porcelain or leaden-blue appearance, which is very striking."[7] The disease is transmitted as a dominant mendelian trait, the blue scleras being a more dominant factor than either the brittle bones or the deafness, so that affected persons may be expected to show blue sclerotics in from 90 to 100 per cent of cases and brittle bones with multiple fractures in 50 per cent. Deafness may be expected to occur in 25 per cent of those persons with blue scleras.[8]

CAUSATION

Although the exact cause of the disease is unknown, fundamentally the condition is due to the transmission of a defective gene or genes that characterize normal development of the mesenchyme, so that the problem is essentially one of a genealogic nature. It is the consensus that the disease is a hereditary inferiority of the mesenchyme.[9] Perhaps the defective germ plasm may have resulted from a mutation of a gene or genes under the influence of certain factors in the external environment, so that the potentialities that they once possessed are no longer capable of free expression. The variation, being of a heritable nature, is consequently evidenced in the descendants. There is no definite proof that the endocrine system is involved or that the mineral metabolism is affected.[10] In the majority of cases the metabolic processes are normal. One fact that seems to be quite consistent is that there is both a quantitative and a qualitative change in the osteoblasts while the osteoclasts are normal.[11]

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5. Levent, R.: Syndrome de Lobstein. Syndrome de van der Hoeve, Gaz. d. hôp. **105**:1901 (Dec. 21) 1932.

6. van der Hoeve, J., and de Kleijn, A.: Blaue Sclera, Knochenbrüchigkeit und Schwerhörigkeit, Arch. f. Ophth. **95**:81, 1918.

7. Rodger, T. R.: Otosclerosis Associated with Blue Sclerotics and Fragilitas Ossium, Proc. Roy. Soc. Med. **29**:1107 (July) 1936.

8. Fraser, I.: Fragilitas Ossium Tarda, Brit. J. Surg. **22**:231 (Oct.) 1934.

9. Hilgenfeldt, O.: Beitrag zum Krankheitsbilde der idiopathischen abnormen Knochenbrüchigkeit, Deutsche Ztschr. f. Chir. **238**:433, 1933.

10. Kraus, E. J.: Osteogenesis imperfecta und endokrines System, Virchows Arch. f. path. Anat. **274**:37, 1929.

11. Cinelli, A. A.: Fragilitas Ossium with Otosclerosis and Blue Sclera, Arch. Otolaryng. **25**:309 (March) 1937.

FORMS OF THE DISEASE

The disease appears in three distinct forms:[12] (1) osteogenesis imperfecta congenita; (2) osteogenesis imperfecta tarda, or the infantile type, and (3) idiopathic osteopsathyrosis. The first two forms are congenital and include the presence of the blue scleras. The third form, or idiopathic osteopsathyrosis, shows the same manifestations as the congenital types with the absence of the blue discoloration of the scleras.

In osteogenesis imperfecta congenita numerous fractures are present at birth, and children with this form of the disease generally die in early infancy. If they survive they invariably remain chronic invalids for life. This is a rare form of the disease.

In osteogenesis imperfecta tarda the only manifestation at birth is the blue scleras. The fractures generally appear only when the child begins to walk. Occasionally the disease may not manifest itself until early adolescence or adult life, or may even remain latent throughout the person's life. This is the most common form of the disease.

Idiopathic osteopsathyrosis is to some extent a self-limited disease; it appears about the age of 3 and follows much the same course as the tarda form, but there are no blue scleras.

PATHOLOGIC FEATURES

The pathologic condition is practically limited to the mesenchyme, so that the bones, muscles, fasciae, ligaments and tendons show the greatest changes.

The bones of the extremities show the greatest degree of involvement. They are shorter, smaller and thinner than normal. There is an extreme degree of thinning of the cortex, a decrease in the cancellous and an increase in the medullary elements.[8] The trabeculae are slender and delicate and widely separated by interstices filled with cellular connective or fibrous marrow. As a general rule, no cross trabeculae are present. The lamellae in the honeycomb lack the uniformity and regularity of normal bone. The architectural framework is greatly altered so that the lines of stress and strain are not ideally adapted to conform with the normal pressure relations.

Most striking roentgenographically is the extremely slender shaft which stands out in contrast to the expanded extremities (fig. 1 *A*). There is considerable disproportion in size of the epiphysis and the

12. Sante, L.: Osteogenesis Imperfecta: Principles of Roentgenological Interpretation, in Manual of Roentgenological Technique, Ann Arbor, Mich., Edwards Bros., Inc., 1940, chap. 7, pp. 106-108. Fairbank, H. A.: Some General Diseases of the Skeleton, Brit. J. Surg. **15**:122, 1928. Knaggs, R. L.: Osteogenesis Imperfecta, ibid. **11**:737 (April) 1924.

diaphysis with widening of the metaphysis.[13] Peculiar cross striations are usually present (fig. 1 *B*). After cure the roentgenograms are normal. Biopsy shows the extreme density and hardness of the bone. It feels and cuts like marble.

Fatty infiltration and phanerosis occur in the muscles, which become atrophic and hypotonic.[14] These changes occur both in striated and in

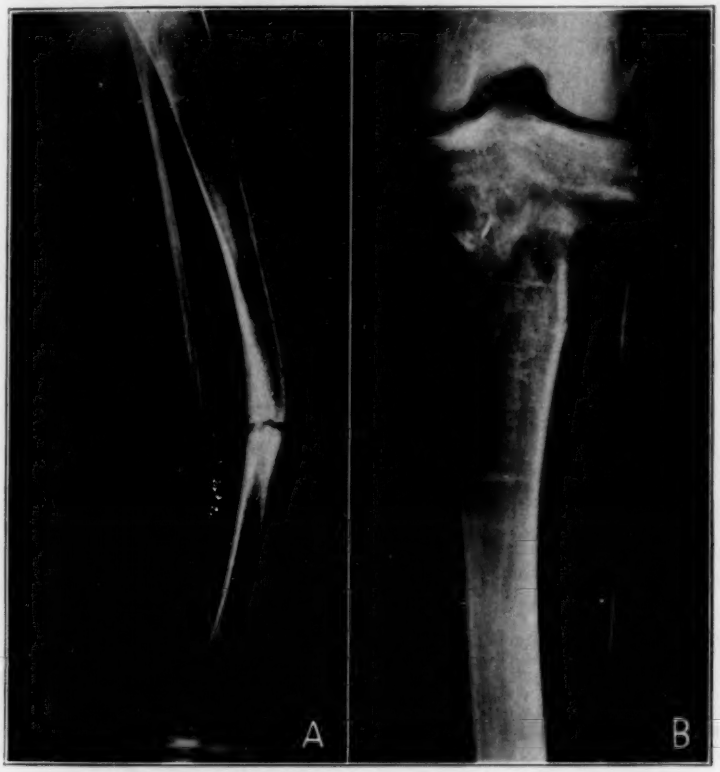

Fig. 1.—Osteogenesis imperfecta. *A*, fracture of the middle of the tibia and fibula in a 9 year old girl (case 4). Note the pathognomonic cross striations in the upper end of the tibia and the narrow bones with a thin cortex. *B*, fracture of the head of the tibia and fibula. Note the cross striations in the upper third of the tibia.

13. Dessoff, J.: Blue Sclerotics, Fragile Bones and Deafness, Arch. Ophth. **12**:60 (July) 1934.

14. Faberi, M.: Sulla patogenesi dell osteogenesi imperfetta, Clin. ostet. **34**:1 (Jan.) 1932.

smooth muscles. The connective tissue likewise becomes altered, so that the ligaments, tendons and fasciae are involved.[15] The walls of vessels, particularly veins, become weak, and varicosities develop. The supporting structures around the joints become lax, and abnormal motility, with frequent sprains and dislocations, results. In the feet, the transverse arch, because of lack of support, gives way, and pes planus results.

SYMPTOMATOLOGY

Osteogenesis imperfecta (hereditary mesenchymal hypoplasia) is characterized by various syndromes and presents the following clinical manifestations:

A. In the bones:
   1. Brittle bones with multiple fractures (50 to 65 per cent) [16]
   2. Curvatures (saber deformity, scoliosis)
   3. Bony prominences on the skull
   4. Bone atrophy
      (*a*) Primary (basic pathologic condition)
      (*b*) Secondary (atrophy of disuse)
   5. Small, short and thin bones

B. In the joints:
   1. Enlargement of the joints
   2. Laxity of the ligaments around the joints
   3. Hypermotility of the joints
   4. Double jointedness
   5. Frequent sprains and dislocations
   6. Pes planus

C. In the eyes:
   1. Blue scleras (90 to 100 per cent)
   2. Corneal astigmatism

D. In the ears:
   1. Progressive otosclerosis (25 to 40 per cent)
      (*a*) Tinnitus (70 per cent)
      (*b*) Vertigo (10 per cent)

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15. Shugrue, J. J.; Rockwood, R., and Anderson, E. W.: Fragilitas Ossium and Deafness, Arch. Int. Med. **39**:98 (Jan.) 1927.

16. Hills, R. G., and McLanahan, S.: Brittle Bones and Blue Scleras in Five Generations, Arch. Int. Med. **59**:41 (Jan.) 1937.

E. In the muscles:
   1. Hypotonia (weakness and flabbiness)
   2. Fatty infiltration and phanerosis
   3. Atrophy
      (*a*) Primary (basic pathologic condition)
      (*b*) Secondary (atrophy of disuse)

F. In the vessels:
   1. Connective tissue changes
   2. Atrophy of the middle coat
   3. Varicosities
   4. Prominence of the superficial veins of the head

TREATMENT

Thus far there is no specific therapeutic agent for this disease. The use of thymus extract and estrogen has been reported to give results.[17] This treatment, however, has usually not been instituted until the child has had one or several fractures. If there is any justification for the treatment at all, it would be a wise procedure to give thymus extract to the mother at about the fourth month of prenatal life, to maintain its use for the duration of pregnancy and if the child is born with the blue scleras to administer it to him during the first few years of life. By adopting such a course of treatment the thymus concentrate would be present during the more formative period of bone development and might predispose to a stronger skeletal structure. The rationale behind such a course of treatment is based on the theory that thymus extract exerts a strong influence on growth and development of bone in prenatal and early postnatal life.[18] There is considerable experimental evidence in support of this concept.[19]

17. Ryan, W. J.: Osteogenesis Imperfecta Tarda, Ann. Surg. **95**:771 (May) 1932; Osteogenesis Imperfecta, with a Suggestion for Treatment, J. Bone & Joint Surg. **14**:939 (Oct.) 1932. Stevenson, G. H., and Cuthbertson, O. P.: Osteogenesis Imperfecta, Lancet **2**:782 (Oct. 10) 1931; cited by Wilson, P. D., and others: Forty-Sixth Report of Progress in Orthopedic Surgery, Arch. Surg. **24**:885 (May) 1932. Gorter, E.: Treatment of Fragility of Bones with Thymus Extract, Nederl. tijdschr. v. geneesk. **73**:2022 (April 27) 1929. Kaplan, E. B.: Multiple Fractures Associated with Blue Sclera, J. Bone & Joint Surg. **16**:625 (July) 1934.

18. (*a*) Gudernatsch, J. P.: The Present Status of the Thymus Problem, M. Rec. **146**:101 (Aug. 4) 1937. (*b*) Rowntree, L. G.: The Thymus Gland, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1938, vol. 8, pp. 519-535. (*c*) Bartoli, O.: Influenza del timo sulla guarigione delle fratture e sulla formazione del callo osseo, Chir. d. org. di movimento **13**:168, 1928.

19. Enriques, P., and Robuschi, L.: Rapporti funzionali tra ghiandole endocrine e frattura ossea, Arch. di fisiol. **24**:382 (July-Sept.) 1926; abstracted, Endocrinology **12**:98 (Jan.-Feb.) 1928. Glässner, K., and Hass, J.: Experimentelle Beeinflussung der Kallusbildung bei Knochenfrakturen, Klin. Wchnschr. **7**:1633 (Aug. 26) 1928; abstracted, Endocrinology **14**:379 (Sept.-Oct.) 1930. Gudernatsch.[18a]

Orthopedic procedures will relieve the deformity and crippling to a large extent. Osteotomy and osteoclasis are the operations of choice, and union occurs after the operations.[20]

The use of homologous bone grafts[21] in patients with ununited fractures or with severe deformities of the bones of the lower extremities, and even in some who are unable to walk or stand, has met with great success. By such an operative procedure hopeless cripples are converted into happy and useful citizens. The application of properly fitting braces, when indicated, is also a valuable procedure.

Prophylactic measures in the way of precautions to guard against possible injury to the bones during infancy, childhood and early adolescence, including the application of braces to the lower extremities in cases of marked weakness of the bone structure, have an important place in the therapeutic regimen.

DIAGNOSIS

Little difficulty is encountered in the diagnosis of the congenital forms when the hereditary factor is present. The diagnostic triad is the blue scleras, the roentgenographic appearance of the bones and the history of the case.

The blue scleras are practically pathognomonic of the syndrome.[16] Other indications associated with blue scleras are tuberculosis, severe anemia and poisoning by metals, particularly lead. At times a bluish tinge is noted in young infants and in some Negro children.

In cases of the congenital form in which the history is negative, the presence of the blue scleras together with the appearance of the roentgenograms will usually suffice for a diagnosis.

In cases of idiopathic osteopsathyrosis the diagnosis is based on the history, appearance of the roentgenograms and histologic studies of the bones if necessary.

Osteopathies that may clinically simulate the disease are rickets, tuberculous and syphilitic bone diseases, bone cysts and osteoporotic changes in the bones.

FAMILY GROUPS AND CASES

Because of the multiplicity of cases, time and space will not permit a detailed account of all, and the discussion of case reports will be confined to those cases that present the most interesting aspects of the disease, the other cases being simply mentioned in order to complete the family tree.

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20. Colonna, P. C.: Osteogenesis Imperfecta, Am. J. Surg. **15**:336-340 (Feb.) 1932.

21. Smith, A. DeF.: Use of Homologous Bone Grafts in Cases of Osteogenesis Imperfecta, Arch. Surg. **34**:687-694 (April) 1937.

Family Group I.—A study of this family group reveals that the condition originated in the family in Ireland in 1825 (fig. 2). The disease was manifested at this time by the presence of deafness and a very small skeletal structure in 1 member. No definite information regarding the scleras in this person could be obtained. There were 7 siblings in the second generation, 1 of whom inherited the disease. Blue scleras, deafness and spinal curvature were the main manifestations of the disease in this person. In the third generation 5 of 9 siblings inherited the condition, and in the last generation 4 cases were found. Deafness was present in every member who inherited the condition.

CASE 1.—J. O., a white man aged 48, single, was admitted to the hospital in March 1939 with the complaint of backache and swelling of the legs of two years' and six months' duration, respectively. He had had deep blue scleras from birth, and a progressive type of deafness had made its appearance at the age of 7. The rest of the history was essentially irrelevant. With the exception of the deafness, every abnormality was found on general inspection. The patient was short and

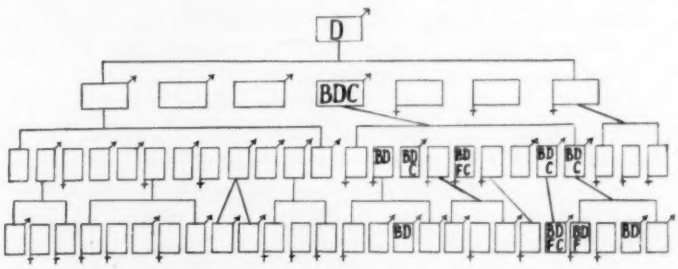

Fig. 2.—Family diagram, family group I. *B* indicates blue scleras; *D*, deafness; *F*, fractures; *C*, spinal deformities.

small boned and weighed 130 pounds (59 Kg.). The scleras were of a striking blue color and of metallic appearance. There were grade 2 scoliosis, with the convexity directed toward the left, and grade 1 lordosis. There was grade 1 edema of both feet and legs, extending upward to a point 10 cm. below the knees. Pes planus, grade 4, was present as a result of ligamentous relaxation. Varicosities of the veins of the lower extremity were noted. There was poor tissue turgor, and the muscles were flabby and hypotonic. The deafness was bilateral and of the conduction type. The result of Rinne's test was positive, and Weber's test showed lateralization of sound to the affected side.

The hemoglobin concentration was 93 per cent; the red blood cells numbered 4,000,000 per cubic millimeter and the white blood cells 10,500. Urinalysis gave normal results. The Kahn reaction of the blood was negative. Phenolsulfonphthalein and concentration tests yielded normal results. A bromsulphalein test gave a normal result. Roentgenograms of the spine showed thinning of the bodies of the eleventh thoracic and first lumbar vertebrae, accompanied by scoliosis. The extremities were normal. A diagnosis of osteogenesis imperfecta tarda (latent form) was made.

CASE 2.—L. O., a woman aged 37, was a sister of the previous patient. Blue sclerotics had been present from birth. She had sustained her first fracture at the age of 3 years. From this time until the age of 18 the patient had had an average of two fractures a year, the bones of the lower extremities being most frequently involved. The tibia, fibula, femur, radius, ulna and humerus suffered multiple fractures. In all, the patient had had twenty-seven fractures. The tibias showed anterior bowing or saber-like deformity. At about the age of 12 years the patient had become hard of hearing. At the time of this study there was bilateral deafness of the conduction type. She heard fairly well over the telephone, however, and she was a switchboard operator, having served in this capacity for the previous seventeen years. At the age of 10 years she could not walk without the aid of crutches, and at the age of 18 years it was necessary for her to use a wheel chair in order to get around. Her scleras were intensely blue; her bones were very small and short, and there was a curvature of the spine. She had had no fractures since the age of 26.

Three other members of this generation, 2 brothers and 1 sister, likewise had the blue scleras, otosclerosis with bilateral deafness, spinal curvatures, short stature and small bones. The deafness made its appearance early. There are 4 other members who are normal. None of the aforementioned 3 members has had fractures, and there are no deformities other than the curvatures.

All 3 of these persons married. In the case of 1 brother, R. O., 4 children were born, 2 normal and 2 with blue sclerotics. The latter 2 children are hard of hearing, deafness having made its appearance at about the age of 8 years. Neither one has curvatures, and only 1 has had fractures. The latter, a girl, has had a total of six fractures, the first making its appearance at the age of 2 years. She is now 12 years of age and has not sustained any fractures for the past two years. Calcium and vitamin D were prescribed and roentgen therapy employed. Four of the fractures were confined to the lower extremities. Good approximation was obtained in every instance, and no deformity resulted.

Two other members of this generation, cousins of the children just described, have blue sclerotics and are deaf, but only 1, a boy, has had fractures. He has had two fractures, both making their appearance before the age of 1. He is now 4 years old.

CASE 3.—D. O., now dead, was the father of the patients in cases 1 and 2. He was one of 7 children, 4 boys and 3 girls. He was the only member of the family affected. Deep blue sclerotics were present from birth; deafness made its appearance at the age of 10 years, was progressive and rendered him almost totally deaf in later life. He had a curvature of the spine, and there was a characteristic limp in his gait. There was no history of fractures. He was born in Ireland and came to this country at about the age of 25. No history of his father could be obtained, other than the fact that he was deaf and very short.

Comment on Family Group I: This family group is illustrative of the hereditary tendency of the syndrome. It is transmitted as a dominant mendelian factor, the blue sclerotics being a more dominant

factor than were the other components of the syndrome. From the discussion of the cases it is readily seen that different factors, as well as various degrees of the same factor, are inherited. What are perhaps two outstanding characteristics in this group are the latent character of the bone conditions and the high incidence of deafness, with its early appearance in every case. Three of the cases are representative of the van der Hoeve syndrome. The intensity of the blue color of the scleras is not indicative of the severity of the bone condition, as is commonly supposed.

Family Group II.—The seat of origin of the condition in this family was Germany, in 1770 (fig. 3). F. B. had blue sclerotics and was deaf; he had 4 children, 3 girls and 1 boy, all of whom had blue sclerotics and were deaf. Deafness did not manifest itself until the

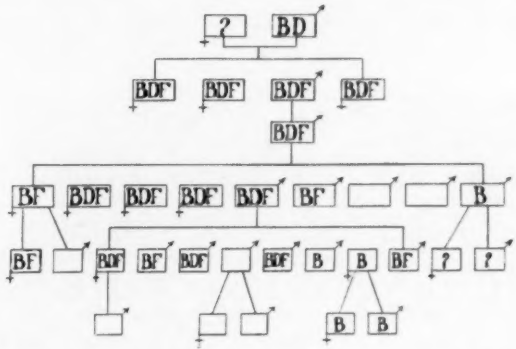

Fig. 3.—Family diagram, family group II. *B* indicates blue scleras; *D*, deafness; *F*, fractures.

third decade. A history of fractures also was obtained for all the 4 children. A discussion of the 3 daughters will be reserved until family group III is discussed, since all 3 married into this family. The boy, J. B., had 1 child, a son, who had blue sclerotics, deep in color, was extremely deaf and had one or two fractures in boyhood. He had 9 children. Seven had blue scleras; 4 of the 7 became deaf between the ages of 25 and 40, and 6 of the 7 had fractures. The incidence of fractures in this family group was not so great. The greatest number that any person had was five. Four girls and 3 boys were affected. Only 2 of the boys and 1 girl married. The girl gave birth to 2 children, 1 of whom had blue scleras and a number of fractures. No information could be obtained concerning the first son. The second son had 8 children, 6 boys and 2 girls. Seven of them had blue scleras, and 5 sustained fractures. Three were deaf. Three of this group

married. One was normal and had 2 children, both of whom were normal. Another, a daughter, with blue scleras, had 2 children, both of whom have the blue scleras but as yet no fractures. They are now aged 2 and 4 years, respectively. A third, another daughter, with the three major characteristics, had 1 normal child, a son.

Comment on Family Group II: The strong hereditary tendency is observed in this family group. Out of a total of 33 members, 23 have the blue scleras, 16 of whom sustained fractures and 12 of whom were deaf. The deafness was strongly inherited, appearing in the second or third decade and rendering the persons almost totally deaf at the age of 45 to 50. The fracture diathesis, while present in 50 per cent of the family group, tended to be less frequent and less severe than usual. This group is likewise representative of the van der Hoeve syndrome.

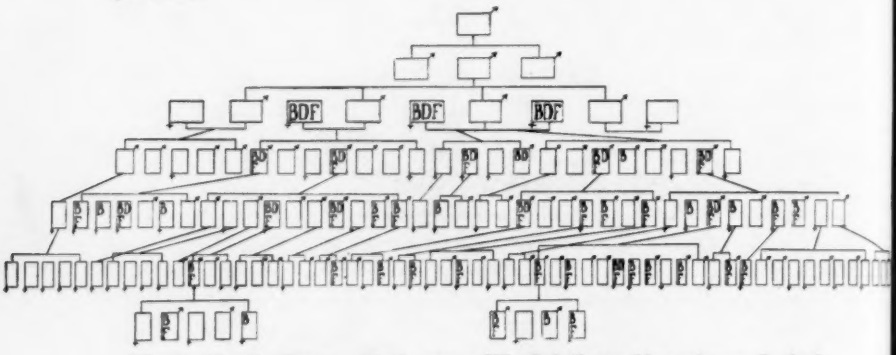

Fig. 4.—Family diagram, family group III. *B* indicates blue scleras; *D*, deafness; *F*, fractures.

Family Group III.—Osteogenesis imperfecta first made its appearance in this family in Maryland and Virginia in 1808 (fig. 4). The ascendants were traced for three generations, to 1735, in England, and the history was entirely negative. There were 4 sons in the third generation, all of whom were normal. Two of the sons married women whose history was also negative for the disease and one of whose families, traced for three generations, were likewise normal. The third son, W. P., married N. B., one of the 3 sisters of family group II; of their 7 children, 2 had the blue scleras, brittle bones and deafness. The fourth son, W. H. P., married S. B., the second sister of family group II, and 2 children out of 4 inherited the condition. After the death of his first wife, W. H. P. married J. B., the third sister of family group II, and of 8 children, 6 boys and 2 girls, 3 boys had blue scleras and brittle bones and 2 were deaf. One of the sons in this generation

had as many as seventy-five fractures. He lived to be 89, and the tendency to fracture persisted until the time of his death. During the last fifteen years of his life he set his own fractures.

Five of the 7 children in this generation who inherited the condition married, and in the next generation there was a total of 38 members, 18 of whom inherited the syndrome. Only 5 of this generation were deaf, however. Eighteen members of this generation married; but 1 of them had no children and is not indicated on the chart; 8 of them had osteogenesis imperfecta. The members who were normal had a total of 28 children, all of whom were likewise normal. A total of 29 children were born to the 8 affected members, and the condition was inherited by 13 of this group. All of these members had blue sclerotics and fractures, and 1 became deaf. The oldest member, however, is only 30, so that for the present a definite conclusion cannot be drawn in relation to the factor for deafness. Two cases in this group are of particular interset and will be considered in some detail.

Fig. 5 (case 4).—A completely incapacitated girl of 9 years with a history of many fractures.

CASE 4.—A girl aged 9 had blue scleras from birth. She sustained her first fracture at the age of 2. This was a transverse fracture of the midportion of the tibia and fibula of the left leg (fig. 1). One year later the tibia and fibula of the left leg were again fractured, at a point 1 inch (2.54 cm.) higher than the previous fracture. Within five months and again in one year fractures occurred in the left leg, the points of fracture being through previously fractured areas. Since then, she has had sixteen other fractures, two confined to the left femur and the rest in the tibia and fibula of the left leg. The slightest trauma was responsible for all the fractures. The child has been unable to stand or walk for the past five years (fig. 5). Except for the use of cod liver oil, no medical therapy has been instituted. The child weighs 60 pounds (27.2 Kg.), is 46 inches (116.8 cm.) tall, is small boned and has pale blue sclerotics and saber deformity of the left leg. There is well developed bilateral pes planus but no scoliosis or deafness.

CASE 5.—R. P., aged 12, a sister of the previous patient, had blue scleras from birth. The first fracture occurred at the age of 1½ years. She has had twenty-five fractures since, all confined to the lower extremities, with the majority in the femurs. There have been no fractures for the past two years. She, like her sister, has been unable to stand or walk since she was 2 years old. The only

therapy has been the use of cod liver oil. The child weighs 75 pounds (34 Kg.), is 54 inches (137 cm.) tall and has small bones, deep china blue sclerotics, saber deformity of both tibias and bilateral pes planus, but no scoliosis or deafness. Both of these girls were born at full term with normal delivery, and both were breast fed.

There are 9 other members of this family, 4 of whom have the blue sclerotics and have had fractures. In addition, 1 boy, aged 3, has a marked frontal eminence; the circumference of his head measures 23 inches (58.4 cm.) (i. e., 4 inches [10 cm.] more than the normal). An older brother and sister have had six and four fractures, respectively. In their cases the predisposition to fractures ceased at puberty. This generation, however, transmitted the condition to the seventh generation, and 5 of 9 members are affected.

Comment on Family Group III: A study of this family further exemplifies the hereditary nature of the disease. Only those persons who were affected with the disease were capable of transmitting it. Although

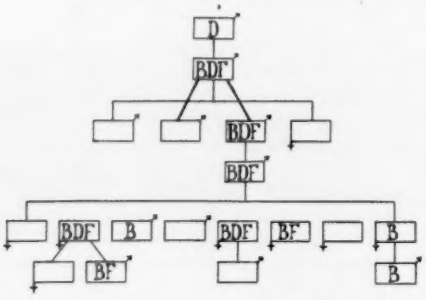

Fig. 6.—Family diagram, family group IV. *B* indicates blue scleras; *D*, deafness; *F*, fractures.

deafness was a promiment feature in the earlier generations, the factor has been rare in the last two generations. The blue sclerotics were inherited, as in all the other families investigated, as a 100 per cent factor in affected persons, the brittle bones with multiple fractures as an 80 per cent factor and otosclerosis with bilateral deafness as a 30 per cent factor.

The spontaneity, frequency and severity of fractures were evident in the last two generations. This fact, together with the scarcity of deafness in these generations, is typical of the Lobstein syndrome. The van der Hoeve syndrome characterized the earlier generations.

Family Group IV.—The history of the condition in this family dates back to 1765 in Germany (fig. 6). G. C. was totally deaf. It could not be ascertained whether he had the blue scleras or brittle bones. He

had 1 child, a boy, who had blue scleras and who also was totally deaf and sustained several fractures. There were 4 children in the third generation, 1 of whom inherited the disease from his father. His scleras were blue; he was deaf, and according to his granddaughter every bone in his body except those of the pelvis and spine had been fractured at one time or another during his life. There was an only child in the fourth generation, and he likewise inherited the syndrome. He broke his legs seven times from slight falls during his childhood, and progressive deafness made its appearance in the third decade, as it had done in the others.

In the fifth generation of this family group there were 5 children in a family of 8 who inherited the blue scleras. Three of the 5 have had fractures, and 2 of the oldest ones affected are slightly deaf. Two of the children have had three fractures each, always in the lower extremities. The third child will be considered more in detail.

CASE 6.—V. C., aged 25, has had blue scleras from birth. At the age of 2 years she sustained a fracture of the femur from a trivial fall while she was toddling about the floor. A short time later another fall caused a fracture of the tibia in the opposite leg. Since then she has sustained numerous fractures of the lower extremities, both femurs and both tibias and fibulas being involved at different times, making a total of twenty-five fractures in all, and always from some slight fall or other trivial cause. Considerable angulation occurred at the fracture sites, with resulting deformity, so that the patient could scarcely walk. Orthopedic measures were then instituted, and several osteotomies were performed, accompanied by straightening of the legs and the application of braces to hold them straight. The braces were kept on for two years, during which time the patient was able to walk some distance to school every day. Four weeks after the removal of the braces the patient was able to walk as well and as readily as a normal child. This child was converted from what seemed an almost hopeless cripple into a bright and happy girl with perfectly good, useful legs.

The fractures in all 3 children had their onset at the age of 1½ years, and the tendency toward fracture ceased at the age of 14. This is a characteristic occurrence in the majority of cases, but it is unusual to observe it repeatedly in a single family.

There are 2 of 4 members of the sixth generation affected. One is 3 months old and has the blue scleras; the other, 2 years old, has the blue scleras and has had one fracture. The mother of the 1 normal child is the patient, V. C., in case 6.

Comment on Family Group IV: The distinguishing characteristics in this family group were the multiplicity and extensiveness of fractures in the case of the son of the third generation, the high incidence of deafness, inherited as a 67 per cent factor by those who are affected, and the favorable response of the patient V. C. (case 6), of the fifth generation, to orthopedic treatment.

Family Group V.—Blue sclerotics made their appearance in this family in Washington, D. C., in 1904. The affected person, now 33, was born at full term with normal delivery, was breast fed and had a normal infancy and childhood. The scleras were blue from birth. She has never had a fracture, and there is no impairment of hearing. She has 1 child, a girl aged 8 years, who has had four fractures and whose scleras were likewise blue at birth. The child was born at full term with forceps delivery after a twenty-four hour labor, was breast fed and had a normal infancy. She suffered her first fracture at the age of 3. She has had none since March 1937. The child has had roentgen therapy and has taken cod liver oil and calcium lactate. No deformity is present, and there is no impairment of hearing. The maternal and paternal ancestors were traced for two generations, with negative results. No history could be obtained beyond the two generations.

Comment on Family Group V: There is no doubt that the child has the syndrome of Lobstein, consisting of blue sclerotics and brittle bones, and it is evident that she inherited the condition from her mother, who has only the blue scleras. Since no other history of the disease could be obtained, it must be admitted either that her mother was the first one in the family to be affected or that the disease skipped two generations, as occasionally happens.[7]

Family Group VI.—The first and only instance of osteogenesis imperfecta in this family occurred in Washington, D. C., in 1904.

Case 7.—N. B., a white physician aged 35, married, who was born at full term with normal labor and delivery, has had china blue sclerotics from birth. His first fracture made its appearance at the age of 10 months. From then until the time of puberty he sustained thirteen or more fractures, all confined to the lower extremities and involving the tibias, fibulas and femurs. Slight trauma provoked the fractures in every instance. Two years after the onset of puberty the tendency for spontaneous fractures ceased, and the patient, being very active and energetic, engaged in all forms of sports, including football. As a result of this activity he suffered seven fractures, all of which were confined to the upper part of the body and included the radius, ulna, clavicle and nose. After his athletic activities, there was a latent period of about ten years during which no fractures occurred. His next fracture was the result of a fall, causing him to break the left ulna. His last episode of fractures happened seven years ago, when a friend jokingly slapped him on the back and broke three ribs.

A careful search of his ancestry, both maternal and paternal, was made. The history went back three generations on the maternal side and five generations on the paternal side. The ancestral, as well as the family, history was negative; the patient's own brothers were normal. The patient has no children. He comes from a good family stock and is well educated, holding several college degrees. The present weight is 160 pounds (72.6 Kg.); the height is 63 inches (160 cm.); the bones are small, but the general development is good. China blue sclerotics and saber-like deformity of the left forearm are obvious. There is no other deformity, and no impairment of hearing exists.

Comment on Family Group VI: An isolated instance of the disease, such as this case represents, is extremely rare,[22] and in view of the hereditary and familial nature of the disease its occurrence requires an explanation. There are three possibilities: (1) that the disease is not always hereditary, (2) that more than two generations may be skipped and (3) that this case represents the source of origin of the disease in this family. The last possibility is the more likely, since obviously the disease must make its initial appearance before it can be transmitted. If there are any children in this family, half will be expected to inherit the condition.

Family Group VII.—Only 1 member of this family group was found to have the disease. The ascendants, descendants and collaterals were traced for three generations on both the maternal and the paternal side. The patient herself, who was born in Virginia in 1896, had 7 siblings, all of whom were normal.

Case 8.—R. T., an unmarried white woman aged 44, was first seen in the medical clinic of the dispensary of the Georgetown University Hospital in March 1940. Her chief complaint was of dizziness, ringing in the ears and slight nausea, dating back ten years. Attacks of these symptoms had occurred periodically, without apparent cause. About six months after the onset of tinnitus in the left ear the ringing was noticed in the right ear. A slight degree of deafness had developed in the left ear when the patient was 25. This was followed five years later by impaired hearing in the right ear. The deafness became progressive until now there were total loss of hearing in the left ear and marked impairment in the right.

The patient had been small and delicate from birth. She had had a normal birth and infancy and was bottle fed. She had had the usual diseases of childhood but had never been seriously ill. Vision had been poor for the past ten years. The patient had been hospitalized four years before for two fractures received in an automobile accident. She had been examined in the eye and ear clinics and in the neurologic clinic twice during the preceding seven years. A diagnosis of chronic otitis media and labyrinthitis with Ménière's syndrome had been made two years before.

The patient weighed 83 pounds (37.6 Kg.) and was 5 feet (152 cm.) tall. The following abnormalities were noted: metallic blue scleras, small bones, pigeon-shaped chest, slightly enlarged knee joints, anterior bowing of the left leg, club-shaped deformity of the left foot, hypermotility of the joints, prominence of the superficial veins of the legs, extremely poor tissue turgor and muscle tone and bilateral deafness of mixed type. Air conduction showed a greater degree of impairment than bone conduction. The result of the Rinne test was negative, and Weber's test showed lateralization of sound to the left. Schwabach's test showed reduction in both high and low tones, the tone limit

22. Parnall, E.: Osteogenesis Imperfecta, J. Bone & Joint Surg. **19**:228 (Jan.) 1937.

being reduced from above and below. Concomitant divergent strabismus of the alternating type was present.

The results of urinalysis and a hemogram were normal. The Kahn and Wassermann reactions of the blood were negative. Roentgenograms of the left leg made at the time the fractures were sustained showed a transverse fracture of both the tibia and the fibula an inch (2.5 cm.) below the knee joint. There was an extreme degree of thinning of both bones; the peculiar cross striations of osteogenesis imperfecta were present but not marked.

Comment on Family Group VII: This isolated case well exemplifies the van der Hoeve syndrome. The deafness not only was progressive and severe but was accompanied by tinnitus, vertigo and nausea, which were very disturbing. The main symptoms were the result of involvement of the eighth nerve, due to the otosclerosis that often accompanies the disease. Although the roentgen appearance of the bones was typically that of osteogenesis imperfecta, the bone condition remained latent and spontaneous fractures did not occur. This persistence of the osseous features, even in latent form, until the age of 40 is extremely unusual. Evidently, either the blue sclerotics had gone unrecognized all the while, or if recognized they were not regarded as important enough to warrant comment.

SUMMARY AND CONCLUSIONS

Osteogenesis imperfecta is a hereditary and familial disease and is transmitted as a dominant mendelian factor. It is a hereditary mesenchymal hypoplasia due to a disturbance of the gene or genes that determine normal mesenchymal development.

The most important features representative of the clinical manifestations of the disease are: (*a*) blue sclerotics, 100 per cent; (*b*) brittle bones with multiple fractures, 65 per cent, and (*c*) otosclerosis with progressive deafness, 43 per cent. The most common deformities are spinal curvatures, saber-like deformity of the long bones and pes planus.

Blue sclerotics may be the only manifestation of the disease, and when associated with a history of other manifestations in other members of the family group they are pathognomonic of the syndrome. In the absence of obvious causes of blueness of the scleras they are pathognomic even when such a family history is not obtainable.

The intensity of the blueness of the scleras is not necessarily an index of the severity of the disease.

Certain families have a predilection in regard to the frequency, severity and time of onset of otosclerosis.

Certain families have a predilection in regard to the incidence of brittle bones with multiple fractures, but there is considerable variation in the occurrence of this factor even in individual families.

With few exceptions there is a marked remission of the tendency toward fracture at the onset of puberty. Adults rarely show the roentgenographic features of the disease. The osseous abnormality is the only reversible feature of the disease.

Multiple fractures at the same site often result in deformity and incapacitation.

The roentgenographic appearance of the affected bones is characteristic, consisting of diminution in size of the diaphysis, great thinness of the cortex and presence of peculiar cross striations.

The early institution of proper orthopedic measures can do much to relieve the crippling nature of the disease.

The economic background does not play a predisposing role in the appearance of the disease.

Of 255 members of 7 family groups, there were 91 who were definitely known to have the disease. The existence of the disease in some of these family groups was traced back for six generations. In each of 2 family groups, only 1 person with the disease could be found, and in a third only a mother and her daughter were discovered to have the disease.

Although there are three recognized forms of the disease, every case in this series is an example of the osteogenesis imperfecta tarda or the infantile type, with the appearance of Lobstein's syndrome as a 57 per cent factor and van der Hoeve's syndrome as a 43 per cent factor.

The prenatal and postnatal use of thymus extract has been suggested.

Future progress in the treatment of the disease may depend on a better understanding of the principles of genetics and eugenics.

NOTE.—Since this paper was accepted for publication we have discovered a new family group in which 7 cases of osteogenesis imperfecta were found. The condition made its appearance in this family in North Carolina, in 1870. Three members of the first generation had blue sclerotics and were deaf, but a history of fractures could not be obtained. Four members of the second generation inherited the condition; all had blue sclerotics, 3 were deaf and 2 had fractures. One of these 4 was the patient who applied for examination. She had blue sclerotcis and was deaf. She has had 2 children, who are normal. Another member of the same generation, who had blue sclerotics and deafness, had 2 children, who are normal. Dislocations were a prominent feature in this family group. Three members of the second generation had dislocations of the left shoulder joint. The patient who was examined had four dislocations, a sister had seven dislocations and a brother had one dislocation.

OBESITY

ITS PATHOGENESIS, ETIOLOGY AND TREATMENT

JULIUS BAUER, M.D.
HOLLYWOOD, CALIF.

CRITIQUE OF THE CURRENT ENERGY THEORY OF OBESITY

The usual conception of obesity, particularly in the United States, is that it is always caused by an imbalance between intake and output of energy. "Exogenous or simple obesity is the result of maladjustments between food and exercise. Endogenous obesity is due to the lowered metabolism resulting from a disturbance in hypothalamic or endocrine functions, e. g., gonads, pituitary, or thyroid" (Best and Taylor,[1] page 981).

According to Means,[2] both the exogenous and the endogenous type of obesity are due to a simple disproportion between the intake of food and the energy requirement of the body. Endogenous obesity is endogenous merely in the sense that in the creation of such a disproportion a fall in the rate of oxidation in the body plays a role. A much greater proportion of obesity, however, is of the exogenous type. As a matter of fact, the ratio between total caloric intake and total caloric output is what counts. Persons who gain weight readily, even though they apparently do not eat to excess, are usually phlegmatic; they worry less, sleep either longer or more soundly and when at rest relax more completely than persons of the normal, or thin, type.

This conception of obesity has been substantiated chiefly by Newburgh and Johnston [3] and almost universally accepted on account of its promulgation by leading authorities; yet it is not satisfactory, for the following reasons:

1. As nobody is in doubt that the law of conservation of energy holds also for the animal body and as it is an established fact that any surplus of intake of energy as compared with its output leads to accumulation of

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From the Department of Medicine of the Louisiana University School of Medicine.

1. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 2, Baltimore, Williams & Wilkins Company, 1939.

2. Means, J. H., in Cecil, R. L.: Textbook of Medicine, ed. 4, Philadelphia, W. B. Saunders Company, 1937, p. 659.

3. Newburgh, L. H., and Johnston, M. W.: The Nature of Obesity, J. Clin. Investigation **8**:197, 1930; Endogenous Obesity: A Misconception, Ann. Int. Med. **3**:815, 1930.

fat in the body, obesity may be called the result of an imbalance between energy intake and energy output. Such a statement is a tautology rather than an explanation of the nature of obesity. Many authorities have emphasized the fact that normal persons must be protected against such an imbalance in some way; otherwise the majority would become obese. As a matter of fact, they are well protected. The automatic regulation of intake and output of energy is controlled rather precisely by a number of so-called general feelings, such as appetite, hunger, satiety and the desire for muscular activity or for its restriction, the last being due to fatigue, weakness or exhaustion. But it is not only this nervous regulatory mechanism which tends to maintain the body weight. The thyroid, as well, adapts its activity to the requirement; it restricts the production of hormone and herewith the oxidative processes in the body if an insufficient amount of food intake threatens the maintenance of the balance, and it functions in excess if overfeeding is going to increase unduly the body weight. This adaptative power characterizes the living organism as compared with a physicochemical machine.

2. If exogenous, or simple, obesity is defined as the result of maladjustment between food and exercise, then it requires a breakdown of the mentioned regulatory mechanism, which is represented by endogenous functions of the living body. In other words, an exogenous obesity is always an endogenous one also. I am very much in doubt whether it is possible to produce obesity artificially in a normal person. What may be produced by artificial overfeeding or artificial restriction of muscular activity is a temporary overweight but not a persisting obesity. If I may use this formula, the relation of such a temporary overweight to obesity is rather similar to the relation of a leukocytosis to a leukemia. The capacity and tolerance of the gastrointestinal tract and the automatic regulations of a normal organism will prevent the evolution of a true obesity. All minute calculations concerning the intake and output of energy hold only for a physicochemical machine—all other conditions being equal—but they fail to be applicable for definite conclusions to a living organism with a far developed adaptative power.

3. To attribute stoutness to an increased appetite resulting either from faulty habits of eating (von Noorden, Joslin, Lichtwitz, Labbé and others, cited by Bauer [4]) or from a hereditary abnormality (Wilder [5]) is not quite justified. Appetite is a general feeling serving the organism to build up the necessary quantity of body tissue and to maintain the

4. Bauer, J.: Endogene Fettsucht, Verhandl. d. deutsch. Gesellsch. f. Verdauungs- u. Stoffwechselkr. **9**:116, 1929.

5. Wilder, R. M.: (*a*) The Regulation of the Weight of the Body, Internat. Clin. **1**:30, 1932; (*b*) Disease of Metabolism: Review of Certain Recent Contributions, Arch. Int. Med. **61**:297 (Feb.) 1938.

body weight at an approximately equal level. It is the requirement of the organism, both quantitative and qualitative, which rules the appetite. Appetite for sodium chloride or for calcium, for instance, is influenced by the functional condition of the adrenal or the parathyroid glands, respectively, as Richter and Eckert [6] demonstrated in interesting animal experiments. Putnam, Benedict and Teel [7] produced typical acromegaly and gigantism in a young female dog by treating it for fourteen months with intraperitoneal injections of an extract of the anterior lobe of the beef pituitary containing the growth-promoting principle. The dog acquired a ravenous appetite, but no one is likely to assume that daily intraperitoneal injections of pituitary extract stimulated it. Every one will rather assume that the injections provoked a tendency toward increased proliferation of cells, leading to gigantism and acromegaly, and that this increased cellular activity required a greater amount of energy and in turn led to an unusual intake of foodstuffs. The increased appetite is therefore to be looked on as an interposed factor not directly influenced by the injections but indispensable for the realization of the gigantism and acromegaly which the growth-promoting substance finally produced.

Reed, Anderson and Mendel [8] found that rats treated with thyroxin lost weight in spite of eating almost double (12 Gm. of food daily as compared with 7 Gm. for the controls). Administration of thyroxin undoubtedly increased the appetite, not directly but by the adaptation of the organism to the increased requirement of food. Every physician with any experience knows that the changes of the basal metabolic rate produced by a pathologic alteration of the thyroid are not followed regularly by corresponding changes of the body weight because of the individually different capacity of adaptation of the appetite to the requirement.

Although the existence of a primarily ill trained or hereditarily abnormal appetite causing obesity hardly can be disproved, there is no positive proof of its existence either, and many facts to be discussed here later argue against the validity of such a hypothesis. It is just as possible that an increased appetite is the consequence of the tendency of the body to gain in weight and that it represents only a necessary

6. Richter, C. P.: Salt Taste Thresholds of Normal and Adrenalectomized Rats, Endocrinology **24**:367, 1939. Richter, C. P., and Eckert, J. F.: Mineral Appetite of Parathyroidectomized Rats, Am. J. M. Sc. **198**:9, 1939.

7. Putnam, T. J.; Benedict, E. B., and Teel, H. M.: Studies in Acromegaly: Experimental Canine Acromegaly, Produced by Injection of Anterior Lobe Pituitary Extract, Arch. Surg. **18**:1708 (April) 1929.

8. Reed, L. L.; Anderson, W. E., and Mendel, L. B.: Factors Influencing the Distribution and Character of Adipose Tissue in the Rat, J. Biol. Chem. **96**: 313, 1932.

means for the realization of such a tendency. This would be a complete analogy to the mechanism operating in artificial acromegaly which I have just discussed.

4. The same reasoning holds true for the decreased output of energy in many cases of obesity. The obvious restriction of muscular activity, the avoidance of any superfluous movement, the more or less marked laziness noted in many such cases may be the consequence rather than the cause of the overweight. Only infrequently do persons bedridden for some surgical reason, such as a fracture, acquire more than a slight and temporary overweight during the time of their inactivity. Such a forced restriction of muscular activity does not result in real obesity. An obese man who avoids unnecessary movements is behaving like a normal person who carries about a more or less heavy load. Thus the tendency toward a decreased output of energy is more the consequence than the cause of obesity.

5. Endogenous obesity is considered as an imbalance between intake and output of energy due to a lowered metabolism. Such a mechanism is possible and does not at all mean, as Wilder [5] claimed, that the law of conservation of energy fails to function. However, is this mechanism actually operating in cases of endogenous obesity?

(*a*) The simplest and most common explanation of the imbalance was formerly the assumption of a diminished basal metabolic rate in cases of endogenous obesity with a subsequently diminished energy requirement. No doubt a person with a lowered basal metabolic rate will increase his weight ceteris paribus, that is, if all other conditions remain unchanged. Increasing weight is therefore a frequent symptom in patients with hypothyroidism, and if it does not appear in all cases, it is because the status quo of other conditions is not maintained. Some few cases of obesity are to be explained by a lower basal metabolic rate, and in such cases overweight is actually one of the symptoms of hypothyroidism. In the majority of obese patients, however, one fails to detect a decreased basal metabolic rate and therefore a diminished requirement of foodstuffs.

I do not wish at this point to enter into a discussion of the difficulties of obtaining reliable values for the basal metabolic rate in obese persons but wish merely to emphasize the fact that in the great majority of such persons the rate has not been found to be diminished. In addition, one must recall the not infrequent cases in which even abnormal leanness is associated with a markedly diminished basal metabolic rate, as, for instance, in Simmonds' pituitary cachexia.

(*b*) When it became obvious that it was impossible to explain an apparent endogenous obesity by a diminished basal metabolic rate, an attempt was made to explain the imbalance on the basis of the not infre-

quent reduction of the specific dynamic action of food. If the intake of foodstuffs does not increase the oxidations, as under normal conditions, then, ceteris paribus, overweight must result. But, again, it is the balance of other factors which as a rule is disturbed by adaptative alterations of the body. Persons with a decrease in or practically an absence of the specific dynamic action of food are to be met with not only among the obese but also among the lean or even the cachectic. In addition, the possibility has to be emphasized that a diminished specific dynamic action could just as well be the consequence of obesity, for the reason that the transformation of carbohydrate into oxygen-poorer fat would not require any further intake of oxygen, and in this way the consumption of oxygen would be diminished.

(*c*) Efforts to prove a particular economy of muscular activity in obese persons (Gessler [9]) have failed. The working muscle of an obese person does not require less energy than that of a normal one.

A lowered metabolism has, therefore, not been proved to be the cause of endogenous obesity, except in those infrequent cases in which obesity is one of the symptoms of hypothyroidism. In those cases of endogenous obesity in which a disturbance of the functions of the hypothalamus, the gonads, the adrenal glands or the pituitary is apparently the cause of the endogenous obesity, a lowered metabolism has not been proved to be operating in the pathogenesis.

6. If a simple disproportion between the intake and the output of energy were the actual cause of obesity, then it would be necessary to discriminate between the different foodstuffs only as far as their caloric value is concerned. For the purpose of transformation of energy a calory is a calory; for the purpose of treating obese persons it is not. The experienced practitioner will reduce the intake of carbohydrates and fat but will not reduce the proteins to the same extent. On the contrary, an undue reduction of the protein calories will not only endanger the integrity of the cells but even inhibit a proper reduction of the body weight. It is not only the amount of calories but also the quality of equicaloric amounts of foodstuffs that counts.

7. Still another factor not to be explained from the point of view of a mere energy imbalance is the abnormal water and salt metabolism encountered, as a rule, in the more pronounced cases of obesity and lipomatosis (Zondek, Bauer [4]). Persons with such a metabolic disturbance frequently pass highly concentrated, scanty urine; a total amount of 300 to 500 cc. per day, with a specific gravity of 1.030 to 1.035, is not unusual. If they are given 1,000 to 1,500 cc. of water over a half-hour period, they usually show a marked retention; elimination does not take place in the normal time of four hours, but may be

9. Cited by Bauer.[4]

delayed twenty-four hours or longer (Volhard's test). If they are given 10 Gm. of sodium chloride, they usually retain the salt for two or three days, instead of eliminating it within the normal time of twenty-four hours.

My former co-worker dell'Acqua [10] determined simultaneously the sodium chloride content of capillary and of venous blood from thirty to one hundred and twenty minutes after the intake of 10 Gm. of sodium chloride in 125 Gm. of water. In some persons with uncomplicated obesity (6 among 13 examined), he found notably higher amounts of sodium chloride in the capillary than in the venous blood, the difference ranging from 40 to 15 mg. per hundred cubic centimeters. Similar differences have been encountered only in persons with certain types of renal lesions or with diabetes. The ingested sodium chloride is retained abnormally in the tissues.

Since the retention of sodium chloride and water in obese persons is not caused by impairment of renal function it must be due to an abnormal avidity of the tissues for these substances. That they are chiefly retained in the cutaneous and subcutaneous connective tissue seems probable from the studies of my former collaborator Recht.[11] The McClure-Aldrich test is a delicate indicator of the water content of the skin; the greater the content the more rapid are the resorption and disappearance of an intracutaneous wheal of a physiologic solution of sodium chloride. In a series of such tests Recht found a diminished resorption time in obese persons and also noted marked regional differences in the resorption time in persons with more localized lipomatosis. Those parts of the body surface containing larger amounts of fat showed a more rapid disappearance of the wheals. A dehydrating injection of a diuretic containing mercury, such as salyrgan, which in some cases is followed by a rapid loss of several pounds, was much less effective in the lipomatous regions of the body than in the others. In other words, the tendency of the subcutaneous connective tissue to accumulate larger amounts of fat is apparently associated with a tendency to store water in these particular regions of the skin. In some cases, Recht found the antidiuretic action of posterior pituitary U. S. P. to be unusually intensive and prolonged.

All these statements concerning the water and salt retention in obese persons have been completely confirmed by Wohl [12] in this country:

10. dell'Acqua, G.: Ueber Austauschvorgänge zwischen Blut und Geweben; die capillar-venöse Differenz des NaCl-Spiegels im Blute, Klin. Wchnschr. **8**: 1709, 1929.

11. Recht, G.: Ueber den Wassergehalt der Haut bei Fettsüchtigen: Untersuchungen mit der Quaddelprobe, Klin. Wchnschr. **8**:1748, 1929.

12. Wohl, M. G.: Metabolic Changes and Treatment of Obesity, Am. J. M. Sc. **183**:613, 1932.

namely, the retention in the Volhard test, the high water content of the skin as demonstrated by McClure and Aldrich's test and the difference in the levels of sodium chloride in the venous and the capillary blood after the administration of 10 Gm. of sodium chloride. Wohl found such differences as great as 100 mg.![13]

8. Hetherington and Weil[14] studied the chemical composition of the bodies of rats exhibiting pathologic obesity resulting from hypothalamic injuries. Calcium and phosphorus were considerably diminished and iron frequently diminished in percentage amounts as compared with values for the controls. They stated:

> It would seem that besides the obviously disordered fat metabolism in these cases of adiposity there is a more widespread upset of the body's physiological economy which takes in the calcium, phosphorus and iron exchanges, and possibly other factors as well.

The mere energy concept of obesity cannot account for these changes.

9. All the more does this hold true if the regional differences of fat deposition are considered. The difference in distribution of adipose tissue in both sexes does not need further discussion. In women rather well defined varieties of fat deposits are met with.[15] Most frequently, in about 90 per cent of all women, the distribution of fat is around the hips and on the thighs, the lower part of the abdomen, the buttocks and the back, as illustrated by Rubens' favorite subjects. One may therefore call this variety the "Rubens type." It corresponds to what is also called the "girdle type" of fat distribution. Other women show a particular accumulation of fatty tissue in the trochanteric region, which protrudes from the outline of the body. One may call this variety of obesity the "breeches" or the "trochanteric" type of fat distribution. Some women are annoyed by a more or less marked accumulation of fat in the lower extremities, usually extending from the hips to the knees or the ankles. In some women the excess fatty tissue is limited to the calves or ankles. In the more pronounced cases of this "inferior" type of fat distribution, the fatty masses are arranged like clusters and the skin on the surface of the thighs is subsequently covered with dimples. The opposite, or "superior" type of fat distribution is seen in women with relatively slender legs and abdomen and rather marked accumulation of fat in the back, the upper parts of the arms, the breasts, the neck

13. Wohl did not mention that his studies are merely a repetition and confirmation of the work done by dell'Acqua[10] and Recht[11] in my hospital in Vienna, although he was familiar with their work.

14. Hetherington, A. W., and Weil, A.: The Lipoid, Calcium, Phosphorus and Iron Content of Rats with Hypothalamic and Hypophyseal Damage, Endocrinology **26**:723, 1940.

15. Bauer, J.: Ueber Fettansatz, Klin. Wchnschr. **1**:1977, 1922.

and the face. Sometimes the unusual accumulation is limited to the breasts. As a matter of fact, there are also borderline conditions and combinations of these pure types.

The localized accumulations of fatty tissue are usually described as lipomatosis, but it must be understood that there are no sharp limits between a lipomatosis and a more or less generalized obesity. The mere fact that an abnormal accumulation of fat may show such different localizations must bring into the discussion of the pathogenesis of obesity another factor besides energy imbalance.

That the current, mere energy conception of obesity is unsatisfactory is a feeling expressed by several authorities in this country. Christian,[16] for instance, declared:

> We must acknowledge that in some cases of obesity the cause is obscure. To say that there is one essential cause, overeating, does not explain all cases . . .

In "Oxford Medicine," Howard and Mills[17] summarized their conception of obesity in the following words:

> In conclusion, it would seem that, although the immediate exciting causes of obesity appear to be the ingestion of abnormal amounts of food, or of alcohol, or deficient exercise, yet the underlying basis is probably an obscure endocrine dystrophy, which overthrows the weight-regulating mechanism of the body by an imposed economy of metabolism and consequently excessive storage of fat.

THE BIOLOGIC THEORY OF CONSTITUTIONAL OBESITY

1. *Lipophilia.*—Any satisfactory conception of obesity has, in my opinion, to consider first the unequal distribution of adipose tissue and consequently the variation in "lipophilia" of the subcutis in different parts of the body. In other words, a local factor must exist which influences the fat deposition in particular regions independently of the general energy balance or imbalance. The importance of such a local factor was first emphasized by Guenther (cited by Bauer[18]), who called the particular avidity to store fat "lipomatous tendency," or "lipophilia."

The enormous differences in lipophilia are obvious if one compares the cutaneous coverings on the forehead, fingers and lower part of the abdomen and back, even in the normal person. The lipophilia of a certain part of the skin tends to persist even when the skin is transplanted. Several observations in the literature[15] prove this point: Burns on the back of the hand in young girls, for instance, were treated by grafts taken from the lower part of the abdomen. Many years later, when the

16. Christian, H. A., in Osler, W.: The Principles and Practice of Medicine, revised by H. A. Christian, ed. 13, New York, D. Appleton-Century Company, Inc., 1938.

17. Howard, C. P., and Mills, E. S.: Obesity, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1940, vol. 4, pt. 1, p. 195.

18. Bauer (footnotes 4 and 15).

girls had grown and had acquired a certain degree of overweight, a second operation was necessary for the removal of the big fat pads which had developed in the grafted skin exactly as fatty tissue had developed in the skin of the lower part of the abdomen.

The frequently entirely unequal distribution of adipose tissue in obese persons demonstrates that a local factor must be also involved in the pathogenesis of obesity, whatever the cause of the condition may be.

The term lipophilia indicates a special tendency to deposit fat as well as a special resistance against the mobilization of fat from the adipose tissue. The existence of a different lipophilia in different regions of the body has been concluded from simple clinical evidence.[19] It exists whether or not its biochemical mechanism can be elucidated. Fortunately, its existence and involvement in cases of obesity can be substantiated by a number of facts.

Endeavors to demonstrate qualitative abnormalities in the metabolism of the obese subject have failed, according to Wilder's critical statement, in 1932.[5a] Contradictory results have been obtained by different authors who have studied the respiratory quotient (Arnoldi; Wang, Strouse and Saunders[20]; Hagedorn, Holten and Johansen[21]) and hunger lipemia (Kugelmann[22]; Hetényi[20]). Yet there have been found differences between obese and normal persons pointing toward an increased tendency of the former to store carbohydrates in the adipose tissue rather than glycogen in the liver and muscles. That carbohydrates are deposited in the adipose tissue in order to be transformed into glycogen first and then into fat has been proved by chemical and histochemical methods (Hoffmann and Wertheimer[9]; Loew and Krčma[23]; Richter[24]; Scoz, Baer and Boeri[25]). Von Bergmann and Goldner,[26] Kugelmann[22] and Brentano[27] have made statements suggest-

19. The experiments of Reed, Anderson and Mendel[8] showed that in rats such a local lipophilia has to be considered, too.

20. Cited by Wilder.[5]

21. Hagedorn, H. C.; Holten, C., and Johansen, A. H.: Pathology of Metabolism in Obesity, Arch. Int. Med. **40**:30 (July) 1927.

22. Kugelmann, B.: Untersuchungen zur Fettsucht als ein Problem intermediärer Stoffwechselstörung, Ztschr. f. klin. Med. **115**:454, 1931.

23. Loew, A., and Krčma, A.: Insulin und Nahrungsdepots, Biochem. Ztschr. **206**:360, 1929; Inselorgan und Fettstoffwechsel der Leber, Klin. Wchnschr. **11**: 584, 1932.

24. Richter, F.: Experimentelle Untersuchungen über das Vorkommen von Glykogen im Fettgewebe, Beitr. z. path. Anat. u. z. allg. Path. **86**:65, 1931.

25. Scoz, G.; Baer, P., and Boeri, E.: Insulina e ingrassamento, Arch. di sc. biol. **22**:142, 1936.

26. von Bergmann, G., and Goldner, M.: Funktionelle Pathologie, eine klinische Sammlung von Ergebnissen und Anschauungen einer Arbeitsrichtung, Berlin, Julius Springer, 1932.

27. Brentano, C.: Beitrag zur Physiologie und Pathologie des Ketonkörperstoffwechsels, Ztschr. f. klin. Med. **124**:237, 1933.

ing an abnormally low glycogen reserve in the liver and muscles of obese persons. Creatinuria, which Brentano stated to be an indication of glycogen mobilization in the muscles, is produced more easily and more rapidly in the obese than in the normal person by eliminating carbohydrate from the diet. Obese persons show a higher increase of lactic acid in the blood after slight muscular exercise than do normal persons, a fact which has also been confirmed by my former collaborator Medvei.[28]

Ketonemia and ketonuria depend on the relative proportions of fat and dextrose oxidized together, and more fat, as well as less dextrose, may account for ketosis. After a carbohydrate-free diet has been observed, the ingestion of olive oil increases the amount of ketone bodies in the blood of an obese person more markedly than in that of a normal one (Kugelmann[22]; Lauter and Neuenschwander-Lemmer[29]). This would indicate a lower rate of oxidation of dextrose together with that of the ingested fat in the obese persons.

On the other hand, there is some evidence of an increased stability of the fat deposits in obese persons as compared with those in normal persons. The fat stored in the adipose tissue in the former is not mobilized and made available for the organism so readily in case of need. My former collaborators Paschkis and Buttu[30] found that prolonged hyperventilation, as well as the oral ingestion of large amounts of alkali, both of which produce an alkalosis, raises the level of ketone bodies in the blood of normal persons, but that they are almost or entirely without this effect in obese persons. A ketonemia produced in such a manner is due to mobilization of fat deposits, which apparently, under the circumstances cited, does not take place so readily in obese as in normal persons. Under normal conditions creatinuria following glycogen mobilization in striated muscles, as in hunger, general anesthesia or various infections, is associated, according to Brentano, with a spontaneous endogenous rise of ketone bodies in the blood due to a mobilization of the fat deposits. Some obese persons, however, fail to react with a rise of ketone bodies in the blood during increased

28. Medvei, C. V.: Untersuchungen über den Kohlehydratstoffwechsel der Fettsüchtigen, Blutmilchsäure und Blutzucker bei der Arbeit, Ztschr. f. klin. Med. **122**:607, 1932.

29. Lauter, S., and Neuenschwander-Lemmer, N.: Ueber den Ketonkörpergehalt des Blutes bei Fettsüchtigen und Normalen, Ztschr. f. d. ges. exper. Med. **99**:745, 1936.

30. Paschkis, K., and Buttu, G. D.: Untersuchungen über die Hyperketonämie bei Hyperventilation und anderen alkalotischen Zuständen, Ztschr. f. klin. Med. **123**:764, 1933; Ueber die Ketonkörperbildung beim Fettsüchtigen. (Beitrag zur Pathologie des intermediären Stoffwechsels bei der Fettsucht), ibid. **123**:776, 1933.

creatinuria (Brentano[27]). MacKay and Sherrill[31] studied the ketonuria exhibited during a fasting period by both obese and normal persons. One group of the obese persons whose conditions were classified as endocrinopathies, but which I should call rather endogenous types of obesity, excreted appreciably less ketone bodies than normal persons. In the other group whose obesity was classified as "simple"—apparently of the "exogenous" variety—the ketonuria was as great as, and usually even greater than, in normal persons. MacKay and Sherrill concluded that the first group had some sort of "locked fat." In my own experience, obese persons do not exhibit ketonuria so readily as normal persons if put on a diet poor in carbohydrate.

Hetényi[32] reported experiments on obese subjects showing a markedly lower rise of the lipid level in the blood as compared with normal subjects if large amounts of fat were administered by mouth or subcutaneously or if artificial fever was produced. Even Wilder,[5b] who had been rather skeptical in 1932, stated in 1938, in commenting on these studies of Hetényi:

> These observations seem to indicate that mobilization of fat from fat depots is resisted in obesity and that deposition is accelerated. The condition seems analogous to the increased stability of deposits of glycogen in the liver and in the muscle in von Gierke's disease (glycogenosis). It seems to me that this conception deserves attentive consideration.

This conception is exactly the same as that which I[4] pronounced in 1929:

> Like a malignant tumor or like the fetus, the uterus or the breasts of a pregnant woman, the abnormal lipophilic tissue seizes on foodstuffs, even in the case of undernutrition. It maintains its stock, and may increase it independent of the requirements of the organism. A sort of anarchy exists; the adipose tissue lives for itself and does not fit into the precisely regulated management of the whole organism.

If I may put it somewhat exaggeratedly: A lipomatous subject may die of starvation and still remain lipomatous.

Finally, I want to mention that my former collaborator dell'Acqua[33] studied the amount of lipase present in the adipose tissue obtained from the living person during a surgical operation. The lipase content of the adipose tissue was found to be lower in obese than in normal persons and was lowest in the tissue of true lipomas.

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31. MacKay, E. M., and Sherrill, J. W.: A Comparison of the Ketosis Developed During Fasting by Obese Patients and Normal Subjects, Endocrinology **21**:677, 1937.

32. Hetényi, G.: Untersuchungen über die Entstehung der Fettsucht, Deutsches Arch. f. klin. Med. **179**:134, 1936.

33. dell'Acqua, G.: Ueber den Lipasegehalt des Fettgewebes bei Fettsucht und Lipom, Ztschr. f. d. ges. exper. Med. **71**:245, 1930.

From the foregoing statments it is evident that such an increased lipophilia is associated with an increased hydrophilia, that is, with an increased tendency to retain water and salt. This holds whether the abnormality is limited to particular regions of the body or is more or less generalized. An abnormally high hydrophilia may easily be tested and used as an indicator for an abnormally high lipophilia. This statement is of great practical value. Reduction of salt and fluid in the treatment of obesity is an essential point in my opinion, as in that of every one who has any experience in treating obese persons. It counteracts the manifestation of hydrophilia and, as it seems, therewith also that of lipophilia. In complete accordance with this view, Wohl [12] emphasized the importance of therapeutic dehydration, because thereby an obese subject "not only loses weight but is prevented from accumulating fat." [34]

It is conceivable that an abnormal "hydrolipophilia" may represent the primary disturbance resulting in an increased appetite and a subsequent imbalance between food intake and energy output, with a diminished specific dynamic action of food and even a lowering of the basal metabolic rate. It is the distribution of energy, too, that counts, not alone the rough imbalance between its intake and output.

It is erroneous to consider the adipose tissue merely as a passive storing place for fat and not to recognize that the adipose tissue as a part of the living body has, too, its own physiologic and pathologic processes.

What are the factors determining and influencing the lipophilia of the subcutaneous tissue? Three such factors must be assumed: an autonomous, an endocrine and a nervous.

(*a*) The Autonomous Factor: From the aforementioned facts, particularly from the results of skin grafts transplanted from the abdominal wall to the back of the hand, it is evident that any particular region of the skin has its own autonomous lipophilia which is a hereditary trait and characteristic of the particular region.[35] Physicians who are accustomed to study not only the patient but also his family will notice that identical or similar varieties of female fat distribution are found in other members of the family. The different varieties of fat distribution in women characterize the strain; they represent a hereditary, that is, a constitutional trait. Any such constitutional trait may, under certain

34. Best and Taylor,[1] in their excellent textbook, stated (page 982): "Undue restriction of the water intake is sometimes practised but this appears to be of no benefit and may be a detriment to health." Such a statement of physiologists is certainly not based on personal experience. In some fields clinicians have to teach the physiologists, and not, as usual, the contrary!

35. Bauer, J.: (*a*) Individual Constitution and Endocrine Glands, Endocrinology **8**:297, 1924; (*b*) footnote 15.

circumstances, become not only a familial but also a racial characteristic. The best example is what is called steatopygia in Bushmen, Hottentots and certain strains of sheep. The local accumulation of huge masses of adipose tissue in the buttocks represents an obvious racial characteristic. Sexual selection in man and artificial breeders' selection in sheep have transformed a formerly constitutional into a racial trait.

Hoffmann and Wertheimer [9] fed chiefly carbohydrates to dogs which had lost most of their fat during a previous period of starvation. They found an accumulation of glycogen in the adipose tissue, indicating the increasing storage of fat. Yet the glycogen was not equally distributed in all parts of the adipose tissue, but was found only in those places in which an actual accumulation of fat took place. In the adipose tissue of the orbits and of the soles, which remains practically unchanged during both starvation and fattening, no glycogen deposits could be observed. This experiment throws an interesting light on the autonomous regional differences of lipophilia, as well as on its biochemical nature.

(*b*) The Endocrine Factor: The most obvious influence on the regional lipophilia of the subcutaneous tissue is exerted by the testicles. The testicular hormone inhibits the accumulation of adipose tissue in those parts of the body which represent the chief sites for the accumulation in normal women, such as on the lower part of the abdomen, around the hips, at the breasts and thighs and on the back, where characteristic wide transversal folds of adipose tissue are found in the lateral parts. If the testicular hormone is lacking, the tendency toward accumulation of fat becomes obvious in those parts in which it is checked under normal conditions. Hence the female, or eunuchoid, type of distribution of adipose tissue occurs in castrated men or in those whose testicles have been destroyed by pathologic processes or have undergone atrophy on account of a primary lesion of the anterior lobe of the pituitary gland or of a definite hypothalamic center, or whose testicles were primarily hypoplastic and did not grow at the age of puberty ("eunuchoidism"). Hence, also, the regular female, or eunuchoid, type of fat distribution is present in obese boys in whom the physiologic production of the testicular hormone is not yet sufficient to prevent the accumulation of adipose tissue of the female type. The larger the quantity of fat deposited, the more striking is the resemblance to the female type and the more likely it may be erroneously considered as a sign of Fröhlich's dystrophia adiposogenitalis. This variety of prepuberal fat distribution might well be termed also the asexual, or sexually undifferentiated, type, since it is independent of sex hormones and is equally common in both sexes. Its presence at the prepuberal age by no means justifies the assumption of a gonadal or pituitary insufficiency.[36]

36. Bauer, J.: Common Diagnostic and Therapeutic Errors in the Management of Fat Boys, M. Rec. **151**:89, 1940; footnote 35*a*.

The ovaries have no influence on the regional distribution of adipose tissue.[55a] Castrated women do not differ from normal ones as far as the distribution of adipose tissue is concerned. What is frequently described as the hypogonadal variety of fat distribution, that is, the trochanteric deposit of fat pads, has no causal connection whatsoever with hypogonadism. Such a statement never has been substantiated and is simply copied by one author from another.

On the other hand, it cannot be denied, although hardly proved, that an insufficiency or absence of ovarian function may increase the general lipophilia under certain conditions. The mere energy concept cannot account for the obesity which develops immediately after castration or after the onset of any type of ovarian insufficiency. As a matter of fact, in only a moderate percentage of patients with such insufficiency does obesity actually develop. The ovaries have an influence on the hydrophilia, however. At the beginning of the menstrual period a tendency to retention of water and salt is found in normal women (Heilig [9]). During this time obese women gain in weight or do not respond to the dietetic restriction as they do before and after menstruation.

Insulin has been shown to enhance the deposition of carbohydrates in the adipose tissue (Hoffmann and Wertheimer [9]; Loew and Krčma [23]; Richter [24]; Scoz, Baer and Boeri [25]). This fact throws light on the nature of lipophilia and on the importance of considering the distribution of energy rather than merely the rough balance between intake and output. It is the intermediary metabolism which determines this distribution, and it is the intermediary metabolism which is obviously somewhat different in obese and in normal people. One part of the fattening effect of insulin injections on thin persons is to be attributed to the increased lipophilia of the adipose tissue.

The adrenal cortex has an influence on the lipophilia. The adiposity which occurs, together with other symptoms and signs, in cases of tumors of the adrenal cortex can by no means be explained by a simple imbalance between intake and output of energy; all the more if the characteristic accumulation of the adipose tissue in the face, the neck, the back and the upper part of the abdomen in contrast to the slender extremities is considered. It is a somewhat male type of fat distribution which is brought about in female persons with adrenal cortical tumors.

The pituitary gland has an indirect influence on lipophilia through the intermediation of both gonadal atrophy, in Fröhlich's syndrome, and adrenal cortical hyperactivity, in Cushing's syndrome.[37] It is, however, questionable whether or not the pituitary gland may influence directly

37. Bauer, J.: Was ist Cushing'sche Krankheit? Schweiz. med. Wchnschr. **66**:938, 1936.

the lipophilia of the tissues, as one is justified in doubting the existence of a pituitary type of obesity. Yet if obesity should prove to be caused directly by a functional alteration of the pituitary gland, then, again, only an altered lipophilia, and not merely an altered balance between energy intake and output, could account for its pathogenesis.

It may seem strange to doubt whether a pituitary type of obesity exists at all, when the textbooks and papers of clinical endocrinologists state it to be extremely common and correlate the girdle type of fat distribution with the pituitary origin of adiposity. Nobody has ever given a proof of the correctness of this view. The reason for such an erroneous conception is this: The great majority of women exhibit the girdle type of fat distribution, and the obesity of most of them cannot be proved to be of thyroid, gonadal or adrenal origin. As the authors do not realize any other possibility of explaining the nature of such obviously endogenous types of obesity, they make the diagnosis of pituitary obesity by exclusion without any positive evidence of an alteration of the pituitary gland. The more specialized in endocrinology a clinical writer is, the more dogmatic are usually his statements, and these are transmitted from one textbook or paper to generations of following ones.

(*c*) The Nervous Factor: The nerve supply of adipose tissue seems to regulate its lipophilia. If a peripheral nerve is severed or if other lesions of the peripheral nerves or of the spinal cord exist, an increased deposit of fat may result in those parts of the adipose tissue which get their nerve supply from the injured nerve tissue. Hausberger and Gujot [38] denervated the interscapular pad of brown adipose tissue in mice and rats and found that it rapidly increased in weight by accumulation of carbohydrate and fat. The brown adipose tissue was almost entirely transformed into the usual white or yellow adipose tissue, as the protoplasm of the cells was replaced by fat droplets. This statement has been amply confirmed.[39] In my medical department in Vienna, Adler-

38. Hausberger, F. X.: Ueber die nervöse Regulation des Fettstoffwechsels, Klin. Wchnschr. **14**:77, 1935. Hausberger, F. X., and Gujot, O.: Ueber die Veränderungen in Fett-, Wasser-, Glykogen- und Trockensubstanzgehalt im entnervten Fettgewebe, Arch. f. exper. Path. u. Pharmakol. **187**:655, 1937.

39. Cedrangolo, F.: Azione del sistema nervoso sul metabolismo dei lipidi di riserva, Arch. di sc. biol. **21**:570, 1935. Beznak, A., and Hasch, Z.: Effect of Sympathectomy on Fatty Deposit in Connective Tissue, Quart. J. Exper. Physiol. **27**:1, 1937. Kuré, K.; Oi, T., and Okinaka, S.: Beziehungen des Spinal-Parasympathicus zu der trophischen Innervation des Fettgewebes, Klin. Wchnschr. **16**: 1789, 1937. Bargi, L., and Politzer, M.: L'azione del ormone tiroideo sulla struttura istologica e chimica del tessuto adiposo innervato ed enervato, Rassegna di fisiopat. clin. e terap. **9**:613, 1937; Influenza dell'enervazione sulla struttura istologica e chimica del tessuto adiposo, ibid. **9**:554, 1937.

Mönnich and Tiberi [40] obtained the same results, and unpublished (because incomplete) experiments of Loebl and Hirschfeld seem to reveal a greater content of sodium chloride of the denervated fatty pad than that of the intact side. Diastase has been found in larger amounts on the denervated side (Hausberger [41]). Recent experiments seem to indicate that denervation of the intercapsular adipose tissue in white rats is followed by an increased tendency to deposit fat if a fat of a widely different iodine value is administered in large quantity after a period of starvation (Bauer, Nadler and Schwoner [42]).

These facts point toward an increased lipophilia as the operative factor in cases of so-called cerebral or hypothalamic obesity. Erdheim,[43] many years ago, came to the conclusion that when tumors of the pituitary gland were associated with obesity (dystrophia adiposogenitalis of Babinski and Fröhlich) the obesity was due to compression of certain cerebral centers on the floor of the third ventricle. Camus and Roussy,[44] as well as Bailey and Bremer,[45] confirmed this view on the basis of their animal experiments. Since epidemics of encephalitis have begun to occur, one occasionally meets with cases in which obesity develops as the result of inflammatory damage to these hypothalamic centers. Syphilitic or postvaccinal encephalitis, rheumatic chorea, tumors of the brain or hydrocephalus may produce obesity through the intermediation of a hypothalamic lesion. I observed extreme obesity develop in a young girl after scarlet fever associated with encephalitis. Definite evidence of the hypothalamic rather than of the pituitary origin of obesity occurring in cases of lesions around the hypophysial region has been given by the excellent work of Smith.[46] He succeeded in producing extreme adiposity in rats by experimentally injuring the tuber cinereum without involvement of the hypophysis. He failed, however, to obtain a similar result by removing or injuring the pituitary gland without involvement of the hypothalamic region.

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40. Adler-Mönnich, J., and Tiberi, R.: Untersuchungen zur Biologie des Fettorgans, Wien. Arch. f. inn. Med. **30**:259, 1937.

41. Hausberger, F. X.: Ueber die Veränderung des Gehaltes an diastatischem Ferment im entnervten Fettgewebe, Ztschr. f. d. ges. exper. Med. **102**:169, 1937.

42. Bauer, J.; Nadler, S. B., and Schwoner, A. M.: The Effect of Nervous and Endocrine Influences upon the Fat Deposition in the Subcutaneous Adipose Tissue, to be published.

43. Erdheim, J.: Ueber Hypophysengangsgeschwülste und Hirncholesteatome, Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. (pt. 3) **113**:537, 1904.

44. Camus, J., and Roussy, G.: Experimental Researches on the Pituitary Body, Endocrinology **4**:507, 1920.

45. Bailey, P., and Bremer, F.: Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773 (Dec.) 1921.

46. Smith, P. E.: Disabilities Caused by Hypophysectomy and Their Repair: Tuberal (Hypothalamic) Syndrome in Rat, J. A. M. A. **88**:158 (Jan. 15) 1927; Hypophysectomy and Replacement Therapy in Rat, Am. J. Anat. **45**:205, 1930.

Regarding the aforementioned facts, it seems justified to refer to an increased lipophilia of the adipose tissue as the chief cause of such a cerebral obesity. At all events, such a conception is better substantiated and more satisfactory than Wilder's [5] hypothesis explaining cerebral obesity by an abnormal irritability of centers of the diencephalon, where feelings of hunger and satiety originate. As I pointed out previously, these general feelings are adapted to the quantitative (energy) and qualitative requirements of the organism; they are under normal conditions, of course, ruled by this requirement.

2. *Definition of Obesity.*—I purposely did not try to give a definition of what may be called obesity until I had discussed the complicated matters leading to a better comprehension of the problem. I mentioned the difference between obesity and temporary overweight brought about by an induced imbalance between food intake and energy output. The German language permits a fine distinction between *Fettleibigkeit* and *Fettsucht*. The former defines an actual state of overweight, so to speak, a static condition of what may be called an excessive corpulence; the latter characterizes a dynamic tendency toward overweight. That is what I want to call obesity. Obesity may be defined as the compulsory tendency toward marked overweight due to abnormal accumulation of fat by persons who are left alone to their automatic regulations and are not supervised as far as the intake of food and expenditure of energy are concerned. The more localized such an abnormal accumulation of fat is, the more it is justified to call it lipomatosis rather than obesity. Yet there are no sharp limits between lipomatosis and obesity, as well as between obesity and the particularities of a lateral (pyknic) habitus which may still be considered normal. What has recently been described as "lipedema of the legs: a syndrome characterized by fat legs and orthostatic edema" (Allen and Hines [47]) is merely a not uncommon variety of such a hydrolipomatosis, which has been well known and studied for many years.[48]

Only the definition of obesity as I have given it suits the generally accepted conception of experienced clinicians who include obesity among metabolic diseases. Were obesity merely the result of a simple imbalance between intake and output of energy, it would not be justified to call it a metabolic disease. Corpulence of temporary character brought about by artificial overfeeding or artificial restriction of muscular exercise is not a metabolic disease.

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47. Allen, E. V., and Hines, E. A.: Lipedema of the Legs: A Syndrome Characterized by Fat Legs and Orthostatic Edema, Proc. Staff Meet., Mayo Clin. **15**: 184, 1940.

48. Bauer, J.: (*a*) Innere Sekretion, Berlin, Julius Springer, 1927; (*b*) Die Behandlung der Fettsucht, Klin. Wchnschr. **9**:2161, 1930.

3. *Etiologic Factors in Obesity.*—As I pointed out, there is no such thing as pure exogenous obesity. All obese patients must have at least a certain individual predisposition; that is, they must have a weight-regulating mechanism which is more readily overthrown than a normal one. All obesity is to a variable extent endogenous.

(*a*) Endocrine Obesity: There are cases in which obesity develops as a result of a tumor or other pathologic process in one of the endocrine glands. These cases justify the classification of hypothyroid, hypogonadal, adrenal and pituitary obesity. It is, however, a very small number of cases of obesity in which the condition may be classified as endocrine with full right. A critical analysis is necessary in order to declare an endocrine disturbance as the actual cause of obesity in a particular case.

Castrates and eunuchoids may be tall and slender as well as obese.[49] After the menopause only a moderate number of women, about 20 to 30 per cent, increase in weight. Estrogen or progesterone therapy has practically no influence on obesity. On the other hand, dietetic reduction of body weight without hormonal therapy may regulate a menstrual disorder. This experience has also been had by Wilder[8] and by Evans.[50]

Irregularity of the rhythm or intensity of menstruation, a late or premature onset or cessation of the menses, sterility, abnormality of the growth of hair, the presence of ovarian cysts and uterine fibromas, some diffuse or nodular enlargement of the thyroid and many other signs of abnormal endocrine function do not, in the majority of cases of obesity, indicate the cause of obesity but represent what I have called "endocrine stigmatization."[51] Obesity may have been present from early childhood, long before the abnormality of the ovarian function occurred. Hypertrichosis may persist unchanged after puberty and may be present in other members of the family who are not obese. The enlargement of the thyroid may not show any temporal connection with the onset of obesity and may not be associated with any functional disorder of the gland. Such an endocrine stigmatization therefore merely indicates some deviation in the glandular structure or activity and does not supply a sufficient explanation for a special glandular origin of the obesity.

(*b*) Cerebral Obesity: This variety is even rarer than endocrine obesity if diagnosis is based on undeniable facts, that is, on the evidence

49. Not all animal species gain in weight after castration.

50. Evans, F. A.: Nature of Obesity in Endocrine Disorders, Pennsylvania M. J. **42**:1174, 1939.

51. Bauer, J.: Die endokrin Stigmatisierten, Deutsche med. Wchnschr. **58**: 439, 1932; footnote 48*a*.

of a cerebral lesion being the cause of obesity in a particular case. In an analysis of 275 unselected cases of high grade obesity which I [4] published twelve years ago, there were only 2 instances of cerebral and 5 of endocrine adiposity. In all the rest of the 268 cases such a diagnosis could not be made.

(*c*) Constitutional Obesity: The term "constitutional" indicates any condition which is determined by the germ plasm, that is, any trait, either normal or pathologic, which is due to a particular gene or mendelian unit and is therefore hereditary. In the analysis of 275 cases, 73 per cent were found in which one or both of a patient's parents were obese too. If members of the family other than the parents were included, a hereditary factor was suggested in 88 per cent of the cases. These figures can be approximately confirmed from a material of at least 1,000 cases. The figures are significant even in full consideration of the great frequency of obesity. According to Carey,[52] it has been estimated that 1 of every 5 adults in the United States is overweight. Some authorities, for example, the physiologists Best and Taylor,[1] have claimed that the role of heredity in obesity is more apparent than real. Any experienced physician with open eyes knows that such a heredity cannot but be real (Wilder,[5] Gurney [53]). As a matter of fact, the constitutional character of the obesity in a particular case cannot be ruled out even if no other members of a patient's family can be found to be obese. This follows from the laws of heredity. I wish to stress the fact that in families affected with the hereditary trait of obesity, the condition is not exhibited by all members of the family. If, in spite of the same educational influence and the same environment, obesity develops in some members of a family and not in others, this is in full accordance with the laws of heredity. It does not, however, support the theory that particular habits arising from environment and education may account for an imbalance between food intake and energy output.

If any one were still in doubt whether or not obesity is really inherited, he would be convinced by the following two observations: Christiansen [54] described a family in which 2 sisters had 5 children each. Three and four, respectively, of the two sets of 5 children were rather big at birth. These babies, immediately after birth, displayed extraordinary appetites, grew very rapidly and accumulated prodigious amounts of fat. Only 1 of them survived the first year. Autopsy, performed in 1 case, did not reveal any explanation of the peculiar "macrosomia adiposa congenita," as the author termed the condition. This observation demon-

52. Carey, L. S.: Obesity, M. Clin. North America **23**:1449, 1939.

53. Gurney, R.: The Hereditary Factor in Obesity, Arch. Int. Med. **57**:557 (March) 1936.

54. Christiansen, T.: Macrosomia Adiposa Congenita: New Dysendocrine Syndrome of Familial Occurrence, Endocrinology **13**:149, 1929.

strated again that overfeeding is clearly not the real cause, but rather the compulsory consequence, of the pathologic anlage for obesity. Overfeeding is nothing but the means for the realization of the potentialities of this anlage.

Danforth [55] bred a strain of yellow mice presenting extreme obesity as a hereditary, dominant mendelian characteristic. Neither macroscopic nor microscopic examination revealed any abnormality to explain it. It is particularly interesting, in relation to Christiansen's observation, to note that in Danforth's strain of mice the pathologic anlage for obesity proved to be a so-called lethal factor if it was inherited from both parents, that is, if the mouse was a homozygote in respect to the character.

How does heredity operate to bring about obesity? Which anatomic structures or which functions does the hereditary factor affect? From the previous discussion it is clear that the gene or genes producing obesity do not affect one particular part of the body only, such as the thyroid, the pituitary or other endocrine gland, or some brain center which governs the accumulation of fat or is responsible for the general feelings regulating the balance of energy introduced into and spent by the body.

Without doubt the hereditary factor affects the local lipophilia of the tissues. This is proved by the previously mentioned familial type of regional accumulation of adipose tissue. I recall once more the steatopygia, which is a racial characteristic.

In addition, however, the anlage for obesity seems to operate also through the endocrine glands regulating the lipophilia and the metabolic conditions of the body. Such an assumption does not indicate a particular structural abnormality, an actual disease of one or several glands; it merely points to some functional alteration of the glands cooperating in the production of obesity. This is suggested by the frequent disturbance of various endocrine functions in obese persons and in members of their families. I discussed this fact previously and concluded that such an endocrine stigmatization is not to be looked on as the pathogenetic factor of obesity. It merely indicates some sort of biologic inferiority of the endocrine system.

It is not only a harmless state of endocrine stigmatization, however, which is met with in obese families. It is not exceptional to find a more serious alteration of some gland, such as a tumor, hypoplasia or atrophy, as the result of the biologic inferiority. I know several families in which constitutional obesity is present and in certain members of which tumors of the pituitary gland have developed at an advanced age. In these persons the obesity is not the result of the tumor; it is undoubtedly constitutional and has dated from early childhood. I also know obese families in which the members are obese one of whom is a eunuchoid.

55. Danforth, C. H.: Hereditary Adiposity in Mice, J. Heredity **18**:153, 1927.

In such a case the vicious cycle is obvious: The inherited constitutional obesity is the real cause of the biologic inferiority of the glandular system, and one of the glands became the particular victim of such an inferiority. Hypoplastic testicles may produce on their part the characteristic type of fat distribution and accumulation which is called eunuchoid obesity. In other words, a person with eunuchoid obesity may not be obese because of his gonadal hypoplasia but may display eunuchoidism as a result of a repercussion of the anlage for obesity on his gonads.

It fits well in the general pattern of the activities of genes and their relation to the phenotype if it is assumed that the genes causing obesity exert their influence not only on the local lipophilia of the adipose tissue but also on the endocrine glands and those centers of the central nervous system which regulate lipophilia and dominate metabolic functions, as well as those which are the site of the general feelings ruling the intake of food and the expenditure of energy. The analysis of the relations between the structure of the genotype and that of the phenotype is, in my opinion, the main task of constitutional physiology and pathology. The way in which the marvelous potential energies, represented by the genes and located in the chromosomes, bring about and rule the harmonic system of organs and functions of the living organism must be the chief objective of studies in the field of constitutional physiology and pathology. No matter whether or not this conception is entirely correct, one thing has to be kept in mind. It is that the definite body weight, the amount of adipose tissue deposited in the body, is determined by the germ plasm. The mass of the body as well as its height is determined by genes. All structures and functions involved in producing the mass and the height of the body seem to depend in some way on these genes.

4. *The Relations of Obesity to Other Constitutional Abnormalities.*—In considering an abnormal gene or gene complex as the cause of constitutional obesity, one must ask whether or not something is known about other genes related to the obesity anlage. First a negative statement can be made. The four blood groups have no relation to obesity.

Yet the hereditary factor which produces obesity may be associated with other abnormal hereditary characteristics and may represent in this way only one part of a more complicated abnormal constitutional syndrome. What has been described and discussed rather frequently in the last few years under the name of the Laurence-Moon-Bardet-Biedl syndrome is an association of obesity with polydactylism and syndactylism, retinitis pigmentosa, hypogenitalism, abnormalities of the skull (usually oxycephaly), deficient intelligence and occasionally other degenerative stigmas. Not all of the symptoms are met with in all cases, and a dissociation may be occasionally found in several members of one family.

I [56] have pointed out, as have my former collaborators Aschner [57] and Pool,[58] that the only satisfactory explanation of this peculiar syndrome is an alteration of several hereditary factors probably associated with each other by linkage of genes. This is a term used by geneticists for a persistent association of genes localized in the same chromosome, and therefore exposed more readily to a common alteration.

In a case under my own observation which was reported by Pooi,[58] extreme familial obesity in a 12 year old girl was associated with polydactylism, syndactylism, hypophalangism due to an abnormal fusion of the phalanges, a marked congenital deformation of the skull, to be classified as acrocephaly, and intellectual disorders. This case represents a combination of two constitutional syndromes, the Bardet-Biedl and the Apert syndrome, which is called "acrocephalosyndactylism." At birth the girl had a weight of 6 Kg. (13.2 pounds). This fact justifies consideration of the adiposity as constitutional. It fits into Christiansen's [54] "macrosomia adiposa congenita." At the age of 12 years the weight was 182 Kg. (400 pounds) and the height 157 cm. Two brothers of the mother had a body weight of 160 Kg. (352 pounds) each; a third weighed 110 Kg. (242 pounds).

Another syndrome in which obesity is the leading symptom is the so-called Morgagni syndrome, which is characterized by the combination of obesity with a peculiar hyperostosis frontalis localized on the inner surface of the frontal bone and by some signs of virilism, such as hypertrichosis in women (Henschen [59]). I cannot agree with those authors who try to explain this syndrome as a pituitary or pluriglandular disorder. An association of several abnormal genes seems far more probable, in my opinion, as I have occasionally met frontal hyperostosis as a constitutional abnormality without any other pathologic condition. In some cases frank imbecility or psychoneurotic symptoms are associated with this syndrome, and rudimentary, as well as full blown, forms may be associated with an atypical set of symptoms belonging to the Bardet as well as to the Morgagni syndrome. This is in complete accord

56. Bauer, J.: Problems of Human Genetics, Bull. Johns Hopkins Hosp. **44**: 52, 1929; Constitutional Principles in Clinical Medicine, in Harvey Lectures, 1932-1933, Baltimore, Williams & Wilkins Company, 1934; footnotes 4 and 48*a*.

57. Aschner, B.: Zur Erbbiologie des Skelettsystems. Beiträge zur klinischen Konstitutionspathologie, Ztschr. f. d. ges. Anat. (pt. 1) **14**:129, 1928; Ueber die Arbeitsmethoden der menschlichen Erbforschung, Wien. klin. Wchnschr. **49**:1304, 1333 and 1362, 1936.

58. Pool, F. L.: Zur Entstehung genopathischer Syndrome (Bardet-Biedl-Akrokephalo-Syndaktylie), Wien. Arch. f. inn. Med. **31**:187, 1937.

59. Henschen, F.: Morgagnis Syndrom, Hyperostosis frontalis interna, Virilismus, Obesitas, in Aschoff, L.; Ceelen, W.; Koch, W., and Schürmann, P.: Veröffentlichungen aus der Konstitutions- und Wehrpathologie, Jena, Gustav Fischer, 1937, vol. 9, pt. 2.

with my explanation. Van Bogaert and Borremans [60] described a family whose members were affected with obesity, retinitis pigmentosa, brachydactylism and frontal hyperostosis. The irregular but frequent association of obesity with many different signs of a deviating constitution puts obesity among the other signs of what I have called "status degenerativus." [61] The term indicates an accumulation of many signs of a deviating, and therefore abnormal, constitution in one person.

In this same connection must be recalled the not infrequent association of obesity and biliary concretions, arteriosclerosis, diabetes and arterial hypertension. In the last two conditions the relationship to obesity is probably more intimate than one based merely on a common abnormal degenerative constitution. Hyperglycemia in obese persons frequently disappears after proper reduction of weight (Labbé [9]), and marked arterial hypertension in obese persons may be considerably lowered if the weight is reduced (Aschner [62]). Those are facts of great practical importance.

TREATMENT OF CONSTITUTIONAL OBESITY

Since as physicians we are unable to alter hereditary factors, it might seem that effective treatment of such an inherited constitutional condition as obesity would be impossible. Mendelian factors represent the unchangeable fate of a person, it is true, but we are still able to do a great deal for those whose inherited tendencies lead them to undesirable conditions. We may change the environment indispensable to the realization of the potentialities of the genes, and we may counteract their activity by interfering with the mechanism of the realization.

Many constitutional abnormalities exist which can be practically cured in spite of the impossibility of changing the underlying genes. Surgical procedures can repair polydactylism or syndactylism, a cleft palate and similar abnormalities. If a woman with black hair wishes to change this constitutional characteristic, she merely dyes it. On the other hand, she has to continue to dye it all her life if she wishes to hide it permanently, and the same reasoning holds true for the suppression of the anlage for obesity.

A normal person regulates his intake and output of energy automatically because of such general feelings as appetite and satiety and

60. van Bogaert, L., and Borremans, P.: La forme familiale de la rétinite pigmentaire avec cécité et obésité dite cérébrale (première observation anatomique), Ann. de méd. **39**:54, 1936.

61. Bauer, J.: Vorlesungen über allgemeine Konstitutions- und Vererbungslehre, ed. 2, Berlin, Julius Springer, 1923; Konstitutionelle Disposition zu inneren Krankheiten, ed. 3, ibid., 1924.

62. Aschner, B.: Beziehungen der Fettsucht zu arteriellem Hochdruck, Diabetes mellitus und Cholelithiasis, Ztschr. f. klin. Med. **116**:669, 1931.

because of his normal glandular and nervous functions. A person with a constitutional obesity which he wishes to suppress cannot rely on his automatic regulations and must follow a certain regimen which counteracts them. In other words, the obese person is forced to eat and drink not what he wants but what his physicians consider useful. He cannot rely on his automatic regulations if he wishes to avoid the consequences of his constitutional trait. We are fully aware of the fact that our treatment of obesity cannot be entirely satisfactory so long as we are not familiar with all the abnormalities of the pathologic intermediate metabolism and so long as we have no possible way of influencing the abnormal lipophilia of the fat-accumulating tissue. We can, however, inhibit the abnormal tendency by a number of means.

In no case should obesity be treated without the prescription, first of all, of a dietetic regimen. All other therapeutic procedures are secondary to this one. Not only a general quantitative reduction of calories should be instituted, but their quality should also be considered. Carbohydrates and fat are known to be likely to be deposited as fat, whereas proteins are more readily burned and utilized. They stimulate the thyroid activity and have the greatest specific dynamic action. This sort of fuel increases the flame in the stove more than any other variety.

On the basis of these facts, we put the patient on a diet containing about 1,100 calories, but no more than 20 to 30 Gm. of fat and 85 Gm. of carbohydrate. The rest of the diet consists of such proteins as lean meat, fish, cheese and eggs. I have sometimes had the rather paradoxic experience that patients whose general intake had been increased by the addition of protein calories lost in weight, whereas their former diet, although poorer in total calories, did not have this effect. Proteins in not too small amounts are indispensable in any case in which the body weight is to be reduced, in order to prevent the risk of damage to parenchymatous organs from chronic undernourishment.

It is necessary, too, to restrict the intake of salt to about 2 to 3 Gm. per day and to limit as far as possible the intake of fluids of all kinds. By this treatment alone all obese patients lose up to a certain point. There the weight becomes stationary, partly as the result of water retention.

At this stage thyroid should be given if no contraindication, such as marked tachycardia, cardiac insufficiency or a definite hyperthyroid state, prevents its use. It should be given regardless of the presence or absence of hypothyroid symptoms. It must act here not as a substitute for insufficient thyroid function but as a stimulant for the oxidative processes and the mobilization of water and salt from the tissues. The basal metabolic rate is of little or no value in deciding whether or not thyroid should be given. The general clinical picture, however, is decisive.

The duration and degree of thyroid treatment depend on the tolerance and reaction of the patient. Relatively high doses are advisable for four to six days, and the "thyroid push" should be repeated after several days of rest. This method seems more effective than the administration of small doses of thyroid continuously over long periods.

It is well known that many obese patients react to relatively mild thyroid treatment with tachycardia and increased nervous irritability, so that this therapy must be discontinued before the desired loss in weight has been produced. In such cases small, nontoxic doses of thyroid should be given in combination with intramuscular injections of a protein preparation. The simplest method is the injection of from 3 to 5 or 8 cc. of boiled milk every four to six days. Neither the thyroid nor the protein therapy in itself decreases the body weight; only the combination is effective. It seems that the protein injections determine the direction of the thyroid activity toward the metabolic processes, these being sensitized by the parenterally administered protein.

When the tendency to water retention is obvious, particularly if it is increasing, the use of a diuretic containing mercury, such as salyrgan or merbaphen, is indicated. The administration of the diuretic should be repeated as necessary at intervals of at least four to six days, and the effect can be markedly increased by the production of artificial acidosis through the oral administration of ammonium chloride, in doses of from 4 to 8 Gm. per day, for two or three days before and on the day of the injection of the mercury-containing diuretic. In many cases a "water push," that is, the intake of 1,000 to 1,500 cc. of water within fifteen to thirty minutes, may have the same dehydrating effect as the use of a diuretic. In spite of the delayed elimination of the liquid in hydrophilic obese persons, the exaggerated, though delayed, diuresis and the extrarenal loss of water may produce a considerable loss of weight after twenty-four to forty-eight hours. This method has been described by my former associate Aschner.[63] A similar underlying principle is employed in various spas in which saline waters are used to promote intestinal and renal elimination of water.

The output of energy should be increased as far as possible by the prescription of greater muscular activity, in the form of walking and other physical exercises, with due regard to the patient's cardiac state. Massage is indicated to loosen fatty masses, particularly when they are accumulated in certain regions of the body surface. This is the only, and unfortunately not a very satisfactory, way to determine the sites in which mobilization of fat should take place. Patients with hydrolipomatous legs should wear elastic stockings to prevent the accumulation of water. When huge masses of fat have accumulated, particularly in

63. Aschner, B.: Zur Therapie der Fettsucht, Klin. Wchnschr. **7**:2242, 1928.

the lower part of the abdomen, their surgical removal may sometimes be of great value, though surgical intervention should always be preceded and followed by appropriate general treatment.

The question whether glandular preparations other than thyroid should be used in the treatment of obesity is still widely discussed. My personal experience leads me to say that only estrogen preparations need be taken into consideration, and then only when ovarian insufficiency is clear. They may diminish the tendency toward water retention to a certain extent. They may aid in provoking menstruation when amenorrhea is present. But they have no effect on the obesity itself. The animal experiments of my former collaborators Adler-Mönnich and Tiberi [64] make it seem advisable not to prescribe thyroid and estrogen preparations at the same time, as the effect of the estrogen is checked by the thyroid. I have never seen any improvement in obesity from the use of preparations of the pituitary. The different combinations of glandular substances now available for clinical use are at the best superfluous; such effect as they produce is dependent on the thyroid substance which they contain.

Finally, but not of least importance, one point should be stressed: If the reduction in weight has reached a certain point and a further reduction seems impossible, treatment should be discontinued for several weeks, during which time the weight is kept unchanged by an appropriate diet. The resumption of treatment after this period often results in a further reduction of weight.

Once more I should like to emphasize the necessity of maintaining a dietetic regimen for a long period, if not for the patient's lifetime. His general feelings regulating the intake and output of energy eventually seem to adapt themselves to the prescribed regimen, so that, as a rule, the originally awkward compulsion becomes gradually a habit which is no longer troublesome.

SUMMARY

The current energy theory of obesity, which considers only an imbalance between intake of food and expenditure of energy, is unsatisfactory.

It is the distribution of energy in the body too which counts, not alone the rough imbalance between its intake and output.

The adipose tissue is not merely a passive storing place for reserve fat, but a living and active part of the body, with its own physiologic and pathologic processes.

The tendency of the adipose tissue to accumulate fat (lipophilia) varies widely in different parts of the body and also in different persons.

64. Adler-Mönnich, J., and Tiberi, R.: Zur Wechselbeziehung zwischen Schilddrüse und weiblichen Geschlechtsorganen, Wien. Arch. f. inn. Med. **32**:41, 1938.

Increased lipophilia is as a rule associated with increased hydrophilia (tendency to retain water and salt).

Lipophilia is determined and influenced by (*a*) an autonomous, (*b*) an endocrine and (*c*) a nervous factor.

There is some evidence that the adipose tissue of an obese person differs from that of a normal person inasmuch as it has greater lipophilia and resists more a mobilization of fat.

Obesity is defined as the compulsory tendency toward a marked overweight due to abnormal accumulation of fat by persons who are left alone to their automatic regulations and are not supervised as far as the intake of food and expenditure of energy are concerned.

While obesity is a definite metabolic disease, corpulence of temporary character brought about by artificial overfeeding or artificial restriction of muscular exercise is not.

The cause of obesity is in a very small number of cases an endocrine disturbance or an alteration of certain cerebral centers; in the vast majority of cases it is a particular constitution; that is, an abnormal gene or gene complex.

An increased appetite with a subsequent imbalance between intake and output of energy is the consequence of the abnormal anlage rather than the cause of obesity.

Some more or less typical combinations of the gene for obesity with genes for other abnormal traits are discussed, such as occur in Laurence-Moon-Bardet-Biedl, Apert and Morgagni syndromes.

The treatment of obesity is outlined. It must be chiefly dietetic.

RIGHT-SIDED AORTA WITH DESCENDING AORTA SIMULATING ANEURYSM

URSULA J. ROCHE, M.D.

ISRAEL STEINBERG, M.D.
AND
GEORGE P. ROBB, M.D.
NEW YORK

The importance of roentgenography in the diagnosis of congenital cardiac abnormalities has been greatly stressed within the last two decades.[1] As a result of this trend, there has been an increase in the percentage of aortic anomalies which have been correctly diagnosed during life. However, in spite of routine roentgen studies of the aorta, including esophagrams and roentgenokymograms, the congenital defect is often missed, mainly because the shadow of the aorta cannot be distinguished from the overlying densities of the spine and of the mediastinal structures. This difficulty has recently been largely overcome by the use of contrast roentgenograms of the cardiovascular system.[2] The entire aorta, from its origin deep in the cardiac mass, to its final subdivision into the iliac arteries, can now be visualized with this technic.[3] It is our purpose in this paper to report a case of right-sided aorta which, both by fluoroscopic and by roentgenographic examination, was at first diagnosed as an aneurysm of the aorta. Visualization studies, however, excluded aneurysm by revealing the presence of a congenital abnormality of the aorta, and esophageal studies, after the establishment of the correct

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From the Department of Therapeutics, New York University College of Medicine, and the Third (New York University) Medical Division of Bellevue Hospital.

1. Rösler, H.: Clinical Roentgenology of the Cardiovascular System, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

2. Robb, G. P., and Steinberg, I.: Visualization of the Chambers of the Heart, the Pulmonary Circulation and the Great Blood Vessels in Man: A Practical Method, Am. J. Roentgenol. **41**:1, 1939; Visualization of the Chambers of the Heart, the Pulmonary Circulation and the Great Blood Vessels in Man: Summary of Method and Results, J. A. M. A. **114**:474 (Feb. 10) 1940.

3. Robb, G. P.; Roche, U. J., and Steinberg, I.: Visualization of the Aorta in Disease, to be published.

diagnosis, demonstrated the changes pathognomonic of right-sided aorta which have been described in the literature.[4]

REPORT OF A CASE

T. F., a white man aged 50, entered the Third Medical Division of Bellevue Hospital in December 1939 with an acute infection of the upper respiratory tract. He denied having had hemoptysis, thoracic pain, dyspnea or other symptoms of cardiovascular or pulmonary disease. There was no history of syphilis or any previous illness.

Physical Examination.—On entry the patient did not appear acutely or chronically ill. The head and the neck showed no abnormalities except a sluggish reaction of the pupils to light. The lungs were clear. The point of maximum intensity of the apical beat was in the fifth intercostal space, 8 cm. from the midsternal line; no abnormal pulsations were detected. The heart sounds were normal; the aortic second sound was not accentuated and was greater than the pulmonic second sound. There were no murmurs. The pulse was regular with a rate of 80 per minute. The blood pressure was 118 systolic and 84 diastolic. The abdomen and extremities showed nothing abnormal.

Laboratory Examination.—The erythrocyte count was 4,200,000 per cubic millimeter; the hemoglobin content was 88 per cent; the leukocyte count was 9,300, with a normal hemogram; the Wassermann reaction was repeatedly negative, and results of chemical examination of the blood and of urinalysis were within the limits of normal. The conventional electrocardiogram was normal, showing regular sinus rhythm and no deviation of the electrical axis. Stethograms taken over the aortic, pulmonic and apical areas revealed no abnormality. According to the interpretation of a routine teleoroentgenogram (fig. 1 *a*) there was a huge saccular dilatation of either the ascending or the descending portion of the aorta. It was suggested that the patient might be a suitable candidate for wiring of the aneurysm, and he was referred to us for visualization studies. Contrast roentgenograms, taken with the patient in the frontal, the lateral and the right and left oblique positions (figs. 1 *b*, 2 and 3), demonstrated conclusively that instead of an aortic aneurysm the patient had a right-sided aorta with striking elongation and tortuosity of the descending portion, which accounted for the bizarre shadow that was mistaken for an aneurysm on ordinary roentgenographic study. After the establishment of the correct diagnosis, esophageal studies (fig. 4) made with barium sulfate revealed the pathognomonic inversion of the normal aortic impression on the esophagus.

Conventional Roentgenologic Studies.—Fluoroscopic examination and the conventional roentgenogram (fig. 1 *a*) showed that pulmonary fields were clear. There were apparently two leaves to the right half of the diaphragm, the lateral one moving paradoxically with respiration. The size and configuration of the heart in all views appeared to be within the limits of normal for the patient's age and habitus. A semicircular mass extended out from the mediastinum into the right

4. Evans, W.: The Course of the Esophagus in Health and in Disease of the Heart and Great Vessels, Medical Research Council, Special Report Series, no. 208, London, His Majesty's Stationery Office, 1936.

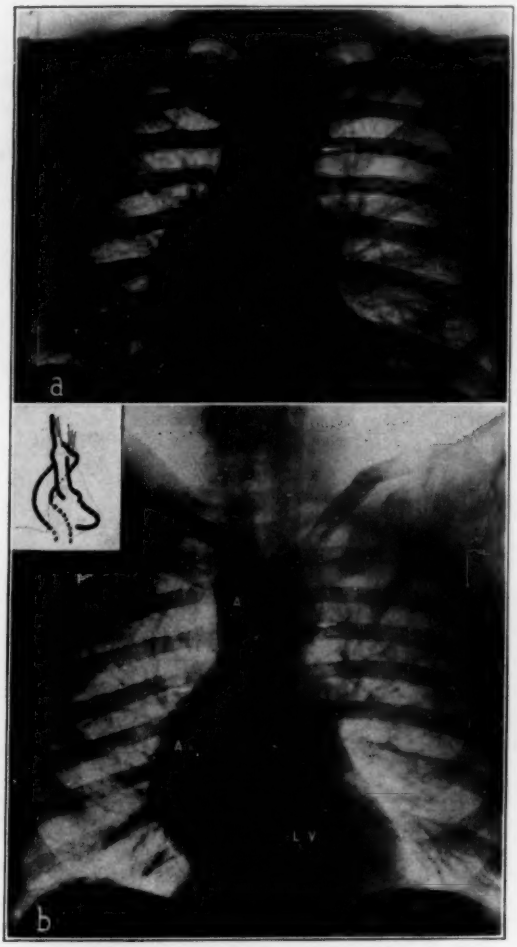

Fig. 1.—(*a*) Conventional teleoroentgenogram, frontal view. The size and the contour of the heart are normal. Note the convex mass along the right side of the mediastinum and the density to the right of the first and second costosternal junctions. The "aortic knob" (white arrow) is small, and the descending aorta is invisible. The left pulmonary artery is unusually prominent.

(*b*) Contrast teleoroentgenogram, frontal view. The left ventricle and the entire thoracic aorta are opaque. The arrow points to the diverticulum. Note the triangle of decreased density between the right border of the ascending and the left border of the descending aorta. In this and in the following figures, A^T indicates the transverse aorta, A^D the descending aorta and LV the left ventricle.

pulmonary field from the level of the second to the sixth rib anteriorly. On fluoroscopic examination, this mass was seen to pulsate. Above it, lying at the right side of the superior mediastinum, there was an ill defined density, while on the left side, slightly below the position normally occupied by the aortic knob, there was a small protuberance. Below this, on the left side, no descending aorta could be seen. In the left lateral view (fig. 5 *a*) the ascending and transverse portions of the aorta were not well seen, while the descending portion was visualized as it pursued a tortuous course in front of and over the spine.

The right anterior oblique view (fig. 4 *b*) showed that the ascending and the transverse portion of the aorta were poorly visualized but that the latter appeared to be behind the trachea, which curved forward at this point. The descending

Fig. 2.—Contrast roentgenogram, left lateral view (target distance 36 inches [91 cm.]). The entire thoracic aorta is filled. The arrow is on the left subclavian artery, pointing down to the diverticulum. In this and the following figures *AA* indicates the ascending aorta.

aorta could be seen overlying the spine much farther to the right than normally, and there appeared to be a fusiform dilatation in its midportion. This portion showed characteristic aortic pulsations, also demonstrated by roentgenokymograms. The fusiform mass could not be seen in the left anterior oblique projection (fig. 5 *b*), and the entire aorta was normal in size. The ascending and the descending limb of the aorta were parallel and in close proximity to each other. The shadow of the aorta in this position looked like a mirror image of the vessel as it is normally seen in the right anterior oblique view.

Esophageal studies in the frontal and right anterior oblique projections (fig. 4) revealed that the esophagus was displaced anteriorly and to the left by the arch of the aorta, which made a concave impression on this structure. Immediately

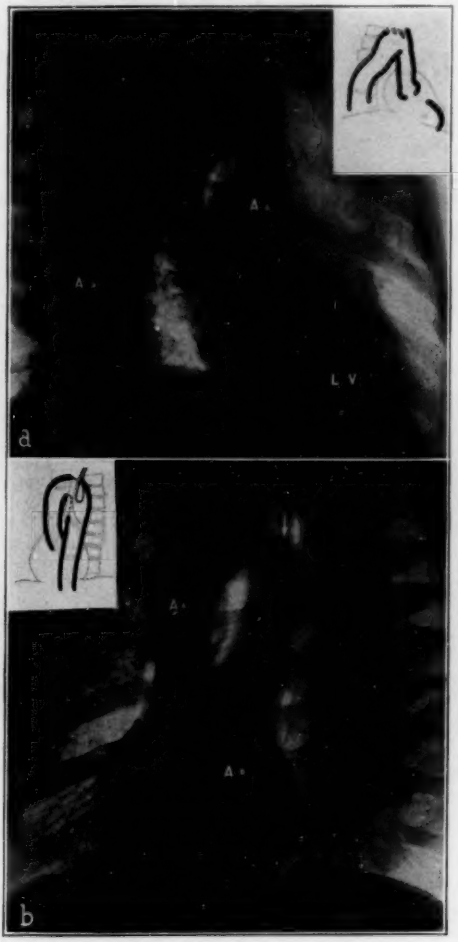

Fig. 3.—(*a*) Contrast teleoroentgenogram, right anterior oblique view, at 45 degrees. The left ventricle, the aortic sinus and the entire thoracic aorta are filled. Note the moderate enlargement of the descending aorta and the absence of aneurysm.

(*b*) Contrast teleoroentgenogram, left anterior oblique view, at 45 degrees. The entire thoracic aorta is filled. The arrow is on the left subclavian artery, pointing to the diverticulum. Note the normal diameter of the ascending aorta and a slight enlargement of the descending aorta.

below this there was a second concavity, while inferiorly the esophagus curved to the right, closely following the course of the convex mass.

Contrast Visualization Studies.—The course of the aorta within the thorax was reconstructed by the correlation of a series of roentgenograms taken in various projections immediately after the injection of radiopaque material. The aorta, arising at the level of the fifth rib anteriorly, ascended obliquely backward and to the right to the first right costosternal junction, where its "knoblike" appearance was clearly seen, as were the vessels to the neck (figs. 1 *b* and 2). It then crossed obliquely downward to the second left costosternal junction, where there was a diverticulum. From this point the aorta curved posteriorly and into the right pulmonary field, describing a large arc, and thence back to the midline near the diaphragm. An end view of the diverticulum, lying immediately behind the trachea,

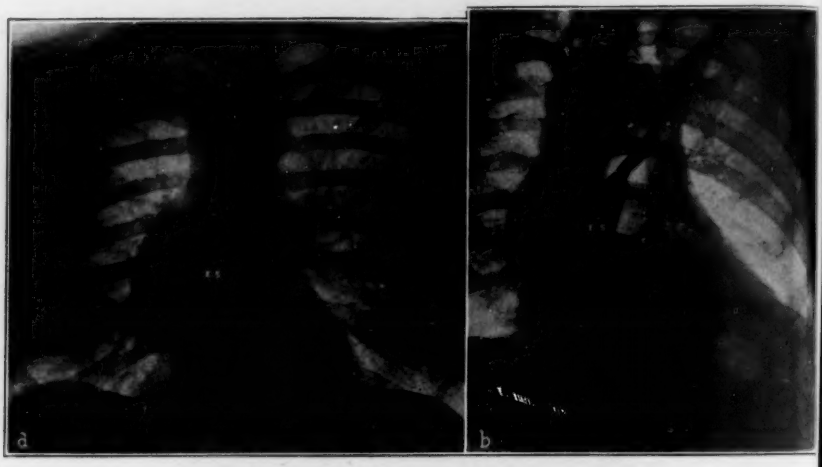

Fig. 4.—(*a*) Esophagram, frontal view. The double indenture of the esophagus by the arch and the descending aorta is visible. The lower one half of the esophagus is displaced to the right. In this and in figure 7, *ES* indicates the esophagus.

(*b*) Esophagram, right anterior oblique view. Note that the esophagus is pushed forward by the arch of the aorta. The descending aorta overlies the spine and appears fusiform.

as well as the origin of the left subclavian artery, could be seen in the left lateral view.

In the right anterior oblique view (fig. 3 *a*) the tortuous course of the thoracic aorta was well demonstrated; furthermore, the position of the arch behind the trachea and the absence of an aneurysm of the descending aorta were shown. Finally, in the left anterior oblique view (fig. 3 *b*) the aorta exhibited no tortuosity or other unusual features except the straightening and the parallel course of the

two limbs and the clearing of the spine by the descending limb. The diameter of the ascending aorta was within normal limits (3 cm.), whereas that of the transverse and the descending portion was larger, measuring 4 cm.

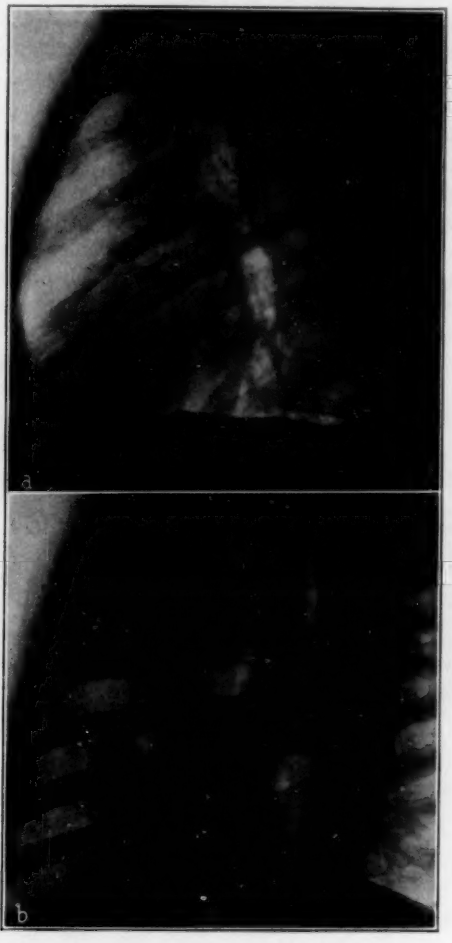

Fig. 5.—(*a*) Conventional roentgenogram, left lateral view (target distance 36 inches [91 cm.]). The thoracic aorta is poorly defined, and the descending portion, overlying the spine, appears tortuous.

(*b*) Conventional teleoroentgenogram, left anterior oblique view, at 45 degrees. Note that the ascending and descending limbs of the aorta are close together. The descending aorta does not overlie the spine.

COMMENT

Up to 1932, 100 cases of right-sided aorta had been diagnosed.[5] In the majority of cases the anomaly was identified at autopsy or in the dissection room, and was rarely recognized clinically. Quain, in his treatise on arteries,[6] mentioned a case of right-sided aorta seen by Sandifort as early as 1793, during a dissection of the thorax. Since Quain's report, numerous examples have been recorded in the literature, mainly in the journals of anatomy.[7] However, it was Assman [8] who, in 1918, first established definite roentgenographic criteria for the diagnosis of this anomaly during life and Arkin [9] who, in 1926, showed that there were additional roentgenographic findings when a right-sided aorta was associated with persistence, in part or in whole, of the left aortic arch. The number of cases detected during life has increased greatly within the last decade, both because of the establishment of these roentgenographic criteria and because of the routine roentgenographic examination of patients with cardiovascular disease and of those presenting the symptom of dysphagia.[10] In 5,000 roentgen examinations of the chest, Biedermann found 7 cases of right-sided aorta.[10a] It is to be expected that the extensive use of thoracic roentgenography today, particularly in tuberculosis surveys, will still further increase the frequency with which this congenital anomaly is diagnosed in patients who are asymptomatic.

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5. Blackford, L. M.; Davenport, T. F., and Bayley, R. H.: Right Aortic Arch: Clinical Report of a Case with Associated Anomalies, Am. J. Dis. Child. **44**:823 (Oct.) 1932.

6. Quain, J.: Anatomy of Arteries, in Elements of Anatomy, ed. 5, London, 1844, vol. 1, pt. 7.

7. (*a*) Reid, D. G.: Three Examples of a Right Aortic Arch, J. Anat. & Physiol. **48**:174, 1914. (*b*) Blackhall, M. A.: Cardiac Malformations with Vascular Anomalies, J. Anat. **62**:227, 1928. (*c*) Stibbe, E. P.: True Congenital Diverticulum of the Trachea in a Subject Showing Also Right Aortic Arch, ibid. **64**:62, 1929. (*d*) Priman, J.: Notes on Anomalies of Aortic Arch and of Its Large Branches, Anat. Rec. **42**:335, 1929. (*e*) Sprong, D. H., and Cutler, N. L.: A Case of Human Right Aorta, ibid. **45**:365, 1930.

8. Assman, H.: Klinische Röntgendiagnostik der inneren Erkrankungen, ed. 3, Leipzig, F. C. W. Vogel, 1924, p. 103.

9. Arkin, A.: Totale Persistenz des rechten Aortenbogens im Röntgenbild, Wien. Arch. f. inn. Med. **12**:385, 1926.

10. (*a*) Spencer, J., and Dresser, R.: Right Sided Aorta, Am. J. Roentgenol. **36**:183, 1936. (*b*) Sprague, H. B.; Ernlund, C. H., and Albright, F.: Clinical Aspects of Persistent Right Aortic Root, New England J. Med. **209**:679-686, 1933. (*c*) Friedman, M.: Right-Sided Aorta: Report of Two Cases, Radiology **25**:106, 1935. (*d*) Fray, W. W.: Right Aortic Arch, ibid. **26**:27, 1936. (*e*) Arkin, A.: Double Aortic Arch with Total Persistence of the Right and Isthmus Stenosis of the Left Arch, Am. Heart J. **11**:444, 1936. (*f*) Bedford, D. E., and Parkinson, J.: Right-Sided Aortic Arch, Brit. J. Radiol. **9**:776, 1936. (*g*) Garland, L. H.: Persistent Right-Sided Aortic Arch, Am. J. Roentgenol. **39**:713, 1939.

While the embryonic development of this interesting condition has been adequately treated in the previous reviews,[11] the development of a right-sided aorta is more easily understood when it is correlated with other abnormalities of the fourth arch. The embryonic development of anomalies of the aorta is diagrammatically represented in figure 6 *a* to *g*. The fourth right arch is represented by *R*, the right dorsal root by *R'* and the left fourth arch and dorsal root by *L* and *L'*, respectively (fig. 6 *a*). If it is postulated that each structure may atrophy in part or in whole, then the following possibilities exist:

1. *R'* may atrophy, leaving *R*, *L* and *L'* intact (fig. 6 *b*). The result can be clearly recognized as the normal human aorta, in which the left fourth aortic arch becomes the definitive aorta and the right subclavian artery is formed from the fourth right arch.

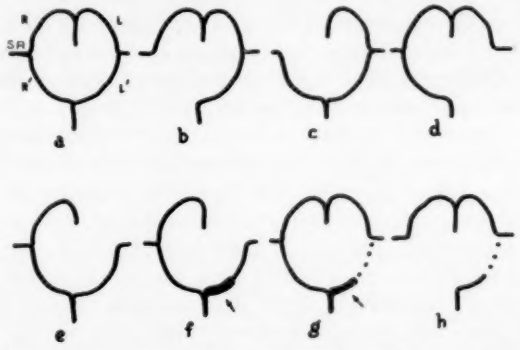

Fig. 6.—Developmental anomalies of the fourth aortic arch. *a*, double aortic arches; *b*, normal left sided aorta; *c*, anomalous right subclavian artery; *d*, simple right-sided aorta; *e*, right-sided aorta with an anomalous left subclavian artery; *f*, right-sided aorta with a persisting diverticulum of the left dorsal root (present case); *g*, double aortic arches with an isthmus stenosis of the left arch; and *h*, coarctation of the aorta (adult type). *R* indicates the right aortic arch; *R'*, the right aortic root; *L*, the left aortic arch; *L'*, the left aortic root, and *SA*, the subclavian artery. The arrows point to the diverticulum.

2. *R* may disappear, resulting in the development of an anomalous right subclavian artery (fig. 6 *c*).[12] In this abnormality, the right subclavian artery has its origin distal to the left subclavian artery and crosses behind the esophagus to reach the right side.

11. Abbott, M.: Right Aortic Arch, in Osler, W., and McCrae, T.: Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 790. Sprong and Cutler.[7e] Fray.[10d]

12. Goldbloom, A. A.: The Anomalous Right Subclavian Artery and Its Possible Clinical Significance, Surg., Gynec. & Obst. **34**:378, 1922. Cairney, J.: Anomalous Right Subclavian Artery, J. Anat. **59**:265, 1925.

3. *L'* may drop out, leaving a mirror image of the first type (fig. 6 *d*). This is the condition described by Assman [6] as simple right-sided aorta with symmetric reversal of the brachiocephalic vessels.

4. *L* may regress, leaving *R*, *R'* and *L'* intact (fig. 6 *e*). The distal segment, L', may be incorporated into the right arch, giving a type of right-sided aorta with four separate vessels to the head. The last of these is the left subclavian artery, which must cross to the left, posterior to the esophagus. This is the mirror image of type 2 (fig. 6 *c*). In some instances, however, the distal segment, *L'*, may dilate and become a diverticulum from which the left subclavian artery takes origin (fig. 6 *f*). This is the type first described by Turner in 1863,[13] and more recently by Arkin,[10e] as right-sided aorta with a diverticulum of the left descending aortic root. The case we have described belongs in this group.

5. Finally, if all segments, *R*, *R'*, *L* and *L'*, persist into adult life there results a double aortic arch (fig. 6 *a*).[14] In this type of anomaly the subclavian arteries are separate vessels on each side. However, there may be partial atrophy of *L'* for a short distance distal to the left subclavian artery, and the remaining portion of *L'* becomes a diverticulum (fig. 6 *g*). This is the type described by Arkin [10e] as a double aortic arch with total persistence of the right arch and stenosis of the isthmus of the left arch. This form of left arch has no counterpart on the right; that is, there has never been seen an itshmus stenosis on the right with total persistence of the left arch. There is a possibility that its occurrence on the left side is due to simultaneous atrophy of the ductus Botalli. Its similarity to coarctation of the aorta of the adult type, in which there is, however, no persisting right arch, can readily be seen (fig. 6 *h*).

Interesting speculations have been advanced as to the cause of these congenital anomalies in man. It has been postulated by some investigators [10e] that right-sided aorta results when the left arch is stenosed in part or entirely before the disappearance of the right arch in fetal life, whereas coarctation of the aorta of the adult type (stenosis of the isthmus) is the result when stenosis occurs afterward. A second, less plausible, theory [15] relates the persistence of the right aortic arch to a change in the amount of cervical flexure in the embryo, causing pressure on the arches lying in the neck in fetal life. This might result in obliteration of the left fourth arch with the right arch left intact.

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13. Turner, W., cited by Thomson, A.: Description of the Dissection of a Case of Right Aortic Arch, Glasgow M. J. **11**:1, 1863.

14. Shaw, D. L.: An Aorta with a Double Arch, J. A. M. A. **28**:538 (March 20) 1897. Harris, H. A., and Whitney, C.: Heart of a Child Aged Nineteen Months Presenting Right and Left Aortic Arches, Anat. Rec. **34**:221, 1927. Lockhart, R. D.: Complete Double Aortic Arch, J. Anat. **64**:189, 1930.

15. Congdon, E. D.: Transformation of the Aortic Arch System During the Development of the Human Embryo, Contrib. Embryol. (nos. 65-71) **14**:47, 1922.

In summary, there may be three main types of right-sided aorta in adult life:

Simple Right-Sided Aorta.—In this type the vessel arises normally, but instead of crossing to the left, it arches to the right and backward over the right bronchus and continues downward slightly to the right of the midline. The brachiocephalic vessels are usually symmetrically reversed, consisting of an innominate artery on the left side and a common carotid and a subclavian artery on the right side. The ductus arteriosus, being the surviving left ductus, must cross behind the trachea and esophagus to reach the aortic arch. The diagnosis rests on the following roentgenographic signs: (1) the presence of an abnormal mediastinal shadow near the first right costosternal junction in the frontal view, associated with absence of the usual aortic knob on the left; (2) the close proximity of the two limbs of the aorta in the left anterior oblique view, as normally occurs in the right anterior oblique projection, and the failure of the descending aorta to overlap the spine, and finally (3) as shown in barium studies, the deviation of the esophagus to the left, instead of to the right, with the aortic impression concave to the right as a consequence.

Right-Sided Aorta with Either an Anomaly of the Left Subclavian Artery or a Diverticulum of the Persisting Left Root.—The first type is unique only in having the left subclavian artery cross from right to left behind the esophagus. In the second type, emphasized by Arkin, the aorta arches over the right bronchus but is joined behind the esophagus by a diverticulum of the left dorsal root and by the dorsal aorta. Here the left subclavian artery arises from the diverticulum and hence does not cross behind the esophagus. The roentgenographic signs are the same as those for simple right-sided aorta, except that the diverticulum may be seen in the frontal view as a small protuberance in the position normally occupied by the arotic knob and in the right oblique view as a rounded shadow within the retroesophageal portion of the aorta. An additional diagnostic point is that the barium-filled esophagus is deviated anteriorly by the diverticulum, a relationship best seen in the right anterior oblique view (fig. 4).[10e]

Complete Double Aortic Arch.—This type is often associated with other congenital cardiac anomalies which are incompatible with life. However, in some instances it has been reported as an accidental finding in autopsies of patients above 50 years of age, but in these it was unassociated with other cardiac abnormalities. In this type, the aorta ascends to the right and turns backward, dividing into two large trunks which enclose the trachea and esophagus in a vascular ring. These vessels unite beyond the insertion of the ductus Botalli to form the descending aorta. From the right, or posterior, arch, the right sub-

clavian and the right common carotid arteries arise, whereas the left subclavian and the left common carotid arteries are branches from the left, or anterior, arch. The diagnosis is made by finding the shadow of the barium-filled esophagus to be uniformly constricted on all sides at the level of the arch of the aorta. When there is a stenosis of the left arch at the isthmus, the left common carotid artery is the first branch of the aorta and the left subclavian artery, being the surviving left fourth aortic arch, is the second branch. It is connected to the left fourth dorsal root, which becomes a diverticulum, by the fibrous band which is the remains of the isthmus. The roentgenographic signs are the same as those of a simple right-sided aorta with a diverticulum of the left dorsal root.

In our patient, the diagnosis of right-sided aorta was not made from examination of the routine frontal roentgenogram of the chest for two reasons: (1) The small shadow caused by the diverticulum occupied the position of the "aortic knob," simulating it, and (2) the pulsating mass on the lower right cardiac border made the diagnosis of aneurysm seem obvious. This pulsating mass projecting from the mediastinum was shown by visualization studies to be a tortuous and elognated descending aorta. Reports of instances in which the descending aorta curves into the right pulmonary field are rare. In a case reported by Rösler and White [16] in which the roentgenogram was similar to that in our case, the abnormal right mediastinal shadow was ascribed to extreme tortuosity of the descending aorta. In that case, too, aneurysm and right-sided aorta were thought to be excluded because the trachea in the frontal view was not deviated to the left. However since esophageal studies were not reported, the presence of right-sided aorta cannot be ruled out conclusively.

Usually, when the aorta elongates, the descending limb, both on the roentgenogram and at postmortem examination, is seen to describe a large arc toward the left lung. Reflection on the relationship of the aorta to the esophagus and the vertebral column makes it clear why this must necessarily take place in most cases. The esophagus is held by fibrous bands to the right of and slightly anterior to the descending aorta, which lies in the left vertebral gutter. Any tendency of the descending aorta to curve into the right pulmonary field will be interfered with by both the esophagus and the vertebral column, and the vessel will be retained on the left side. However, in the case of right-sided aorta this condition is reversed. The aortic arch crosses obliquely backward and to the right, instead of to the left, and the descending aorta lies mainly

16. Rösler, H., and White, P.: Unusual Variations of Roentgen Shadow of Elongated Thoracic Aorta, Am. Heart J. **6**:768, 1931.

to the right of the esophagus. Thus, when the thoracic aorta elongates it will be pushed into the right pulmonary field, pulling the esophagus with it.

In the present case, contrast cardiovascular roentgenograms satisfactorily demonstrated the size and course of the thoracic aorta and showed that the true aortic knob lay near the right upper border of the cardiovascular silhouette. They showed, furthermore, that the shadow misinterpreted as the left aortic knob was caused by a small diverticulum from the left descending root. This diverticulum could be also seen in the left lateral view, in which it was clearly demonstrated that the left subclavian artery arose from this pouch. The tortuous and elongated descending aorta curved into the right pulmonary field, simulating aneurysm of the aorta. When the routine frontal roentgenogram is reviewed, it is easy to see how the correct diagnosis might have been suggested by the shadow at the first right costosternal junction, the hypoplastic "knob" on the left side and the absence of the descending aorta normally present to the left of the midline. The stridor and dysphagia due to pressure on the trachea and on the esophagus, which may occur in this disorder, giving a clue to its nature, were absent in this case. It is possible, however, that more marked arteriosclerosis of the aorta would produce symptoms by pressure on these organs. Finally, other anomalies of the heart and the intrathoracic blood vessels, which sometimes occur with this disorder, were excluded by cardiovascular visualization.

SUMMARY

A case of right-sided aorta with diverticulum from the left dorsal root is described. By contrast visualization of the cardiovascular system, the size and course of the entire thoracic aorta were graphically demonstrated and the nature of the congenital anomaly was established. The pulsating mass near the right cardiac border which simulated aortic aneursym was proved to be the tortuous descending aorta. The embryonic development of right-sided aorta and of other congenital abnormalities of the fourth aortic arch is discussed.

LIFE EXPECTANCY IN CONDUCTIVE DISTURBANCES AFFECTING THE VENTRICULAR COMPLEX OF THE ELECTROCARDIOGRAM

I. GENERAL CONSIDERATIONS OF BUNDLE BRANCH BLOCK WITH CONCORDANT AND WITH DISCORDANT GRAPHS AND THE WIDE S WAVE PATTERN, BASED ON 1,611 CASES

FREDRICK A. WILLIUS, M.D.

THOMAS J. DRY, M.B.

AND

RICHARD REESER JR., M.D.

Fellow in Medicine, the Mayo Foundation

ROCHESTER, MINN.

The reader who surveys critically the present day voluminous literature dealing with bundle branch block and allied disturbances does so with an overpowering sense of confusion and with the realization that that the subject is one demanding clarification and simplification. The majority of published investigations deal either with the experimental production of bundle branch defects in animals or with the study of clinical electrocardiograms shuffled into various classifications by various authors.

Without doubt the outstanding contribution in the field of disturbances of conduction is the careful and painstaking histopathologic investigations of Yater and his co-workers.[1] In fact, with the exception of certain experimental studies on animals, which obviously are not strictly comparable, their work is the only existent groundwork for the comparison and classification of clinical electrocardiograms. Mahaim's [2]

From the Section on Cardiology (Drs. Willius and Dry), the Mayo Clinic.

1. (*a*) Yater, W. M.; Cornell, V. H., and Claytor, T.: Auriculoventricular Heart Block Due to Bilateral Bundle Branch Lesions: Review of the Literature and Report of Three Cases with Detailed Histopathologic Studies, Arch. Int. Med. **57**:132 (Jan.) 1936. (*b*) Yater, W. M.: Pathogenesis of Bundle Branch Block: Review of the Literature; Report of Sixteen Cases with Necropsy and of Six Cases with Detailed Histologic Study of the Conduction Systems, ibid. **62**:1 (July) 1938.

2. Mahaim, I.: Les maladies organiques du faisceau de His-Tawara: Les syndromes coronaire. L'endocardite septale. L'infarctus septal (étude clinique et anatomique), Paris, Masson & Cie, 1931; Nouvelles recherches sur les lésions du faisceau de His-Tawara (deuxième mémoire); le bloc de branche gauche et sa pathogéne; la septite mitrale, Ann. de méd. **38**:185, 1935.

work is also outstanding in this field. Owing to the fact that studies of the conducting system of the heart by means of serial sections consume vast amounts of time and demand extraordinary patience, reliable investigations have been few.

Yater and his co-workers [1] reported 9 cases in which the conduction system was completely studied by serial sections; in 3 cases auriculoventricular heart block was present and in 6 cases bundle branch block. In all of the first 3 cases published (those of auriculoventricular heart block) Yater and his co-workers [1a] concluded that the pathogenic factor was probably disease of the coronary arteries and that the condition is due in most instances to lesions, partial or complete, in both bundle branches, although they expressed the belief that destructive lesions of the terminal portion of the bundle of His may also produce such varying ventricular complexes.

Of the 6 cases of bundle branch block studied by serial section, Yater concluded that both branches were affected in each case, but it was always possible to state which of the two branches was more seriously damaged. The lesion consisted of fibrosis in all cases. In most of the cases it seemed proper to attribute the pathologic condition of the bundle branch and myocardial disease to disease of the coronary arteries. In commenting on the frequency of greater damage to the right bundle branch than to the left in cases of rheumatic heart disease, Yater concluded that perhaps the arteritis of rheumatic causation, involving more prominently the intramyocardial arteries than the large subepicardial vessels, more often affects the entire thickness of the interventricular septum and would be more likely to destroy completely the right bundle branch in its intramyocardial portion than it would the subendocardial portion, that is, the main portion of the extensive left branch. In cases of coronary disease or hypertension or both, the brunt of the strain, either vascular or hypertensive, is borne by the left ventricle; therefore, it is fair to assume that the nutrition of the left bundle branch would be much more likely to suffer severely than that of the right branch. From a study of these 6 cases, Yater expressed the belief that the amplitude of the ventricular complex is not entirely dependent on the state of the bundle branches in the human subject.

It is our intention, in so far as possible, to classify our clinical electrocardiograms according to the system used in the cases published by Yater, in which lesions were demonstrated involving the bundle branches bilaterally and in which one branch was more extensively involved than the other. The electrocardiograms in his first 3 cases were all representative of right bundle branch block. The QRS intervals ranged from 0.12 to 0.16 second, and the amplitude of the complexes varied considerably. However, in all cases the T waves were directed opposite to the QRS

complexes in leads I and III. In these cases the right bundle branch was predominantly involved.

The last 3 cases were all examples of left bundle branch block. The QRS intervals were recorded as 0.13, 0.12 and 0.16 second, respectively; a variation of the amplitude of the QRS complexes occurred, and notching of their components was present in only 1 case. The T waves bore a direction opposite to the QRS complexes in leads I and III. Preponderant damage was demonstrated in the left bundle in the first 2 cases, whereas in the last case only moderate involvement of both branches was found.

In our discussion of bundle branch block we unequivocally accept the new terminology of the condition.[3] Many terms have been used denoting presumed variations in disturbances of cardiac conduction, based largely on electrocardiographic configuration. They comprise "arborization block"; "bundle branch block," typical, atypical and indeterminate, heterogeneous and homogeneous, complete and incomplete; "intraventricular block," and other terms.

Since Carter's [4] designation, in 1918, of definite graphic criteria for the recognition of bundle branch block, the cardiologist has been conscious of a definite electrocardiographic pattern that is glaringly impressive and is a remarkable departure from the normal electrocardiogram and those with lesser graphic variations. Recognition of this distinct form has resulted in the unwillingness of many cardiologists to consider more attenuated forms of this pattern as exemplifying the same condition. Carter's criteria included a widening of the QRS complex beyond 0.1 second and notching, preponderance of the ventricle supplied by the uninterrupted bundle branch, either right or left axis deviation with the dextrocardiogram appearing in cases of left bundle branch block and with the levocardiogram in cases of right bundle branch block (now reversed by present day concepts), exaggeration of the amplitude of

3. Fahr, G.: An Analysis of the Spread of the Excitation Wave in the Human Ventricle, Arch. Int. Med. **25**:146 (Feb.) 1920. Oppenheimer, B. S., and Pardee, H. E. B.: The Site of the Cardiac Lesion in Two Instances of Intraventricular Heart Block, Proc. Soc. Exper. Biol. & Med. **17**:177, 1920. Barker, P. S.; Macleod, A. G., and Alexander, J.: The Excitatory Process Observed in the Exposed Human Heart, Am. Heart J. **5**:720, 1930. Wilson, F. N.; Macleod, A. G., and Barker, P. S.: The Order of Ventricular Excitation in Human Bundle Branch Block, ibid. **7**:305, 1932. Marvin, H. M., and Oughtersen, A. W.: The Form of Premature Beats Resulting from Direct Stimulation of the Human Ventricles, ibid. **7**:471, 1932. Vander Veer, J. B.: Premature Beats Produced by the Mechanical Stimulation of the Exposed Human Heart, ibid. **8**:807, 1933.

4. Carter, E. P.: Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrioventricular Bundle Branches and Their Terminal Arborizations: Clinical and Histologic Report of a Case in Which Such Aberrant Complexes Were Obtained, Arch. Int. Med. **22**:331 (Sept.) 1918.

all ventricular deflections, including the T wave, and the T wave directed opposite to the main portion of the QRS deflection.

Certain modifications of these criteria are now generally accepted, namely, the requirement of complexes of high amplitude is no longer demanded. It is also questionable whether marked notching of the QRS complex is requisite provided that the QRS interval is prolonged to 0.12 second or more.

In 1920 Wilson and Herrmann,[5] in a significant publication, concluded that complete bundle branch block produces characteristic changes in the form of the ventricular complex, both in animals and in man, and accepted Carter's criteria for man as correct. They further concluded that delayed conduction of the impulse through the branches of

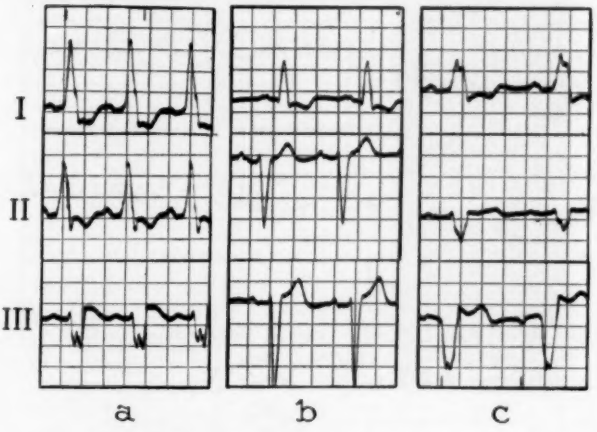

Fig. 1.—Varieties of left bundle branch block with concordant graphs, showing differences in the amplitude of the QRS deflections and in the width of the QRS complexes. In each case the T waves in leads I and III are opposite in direction to the main deflection of the QRS complex, and in each case left axis deviation exists.

the auriculoventricular bundle (incomplete bundle branch block) produces ventricular complexes which are transitional in form between the normal ventricular complex and complexes characteristic of complete bundle branch block.

We believe, in view of the studies of Yater and of Mahaim, that certain modifications of the foregoing concept are desirable. We question particularly the modification of the term "bundle branch block" by the terms "complete" and "incomplete," feeling doubtful whether the

5. Wilson, F. N., and Herrmann, G. R.: Bundle Branch Block and Arborization Block, Arch. Int. Med. **26**:153 (Aug.) 1920.

electrocardiogram is uniformly able to differentiate accurately between complete bundle branch interruption and partial interruption or varying degrees of the latter. This objection is based on the universal bilaterality of lesions of the conduction system and the frequent complete obliteration of one branch, which result in electrocardiograms departing only in accentuation of form from those generally recognized as representative of the classic type of bundle branch block.

It is our contention, therefore, that "bundle branch block" should be represented not only by the classic electrocardiograms universally acknowledged to meet these requirements but also by some of those which have been classed as representing intraventricular block, namely,

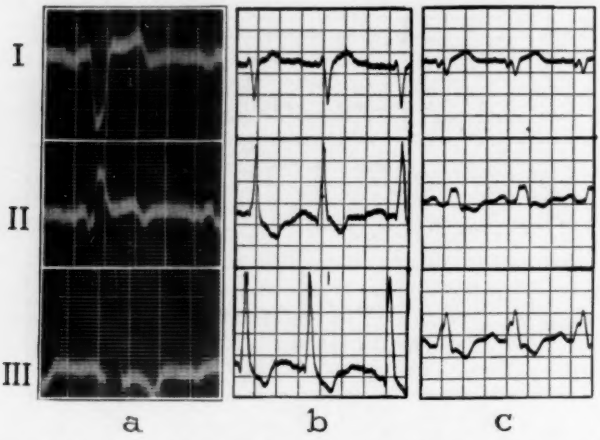

Fig. 2.—Varieties of right bundle branch block with concordant graphs showing differences in the amplitude of the QRS deflections and in the width of the QRS complexes. In each case the T waves in leads I and III are opposite in direction to the main deflections of the QRS complex, and in each case right axis deviation exists.

those of lesser amplitude and with shorter QRS intervals (beyond 0.10 second), with the T wave (figs. 1 and 2) directed opposite to the main deflection of the QRS complex in leads I and III (as in the classic type of bundle branch block); they may show left or right axis deviation according to the branch predominantly affected, without, however, necessarily displacing the typical levocardiogram or dextrocardiogram; notching or slurring may or may not be present. Electrocardiograms exhibiting a spread of the QRS complex beyond 0.10 second, regardless of the amplitude of the ventricular complex, but not associated with directional changes of the T wave opposite to the main deflection of the

QRS complex in leads I and III (fig. 3) and not necessarily associated with definitive axis deviation must still be regarded as characteristic of bundle branch block, but it is our contention that they should be distinguished from electrocardiograms occurring in cases of the classic variety of conduction disturbance as already defined. This separation, indeed, is not artificial, for not only are the electrocardiographic patterns different in their basic configuration but the life expectancy curves of patients who have them are distinctly divergent in their trends.

In keeping, then, with our original aim of simplifying the nomenclature and of avoiding as far as possible the introduction of new termi-

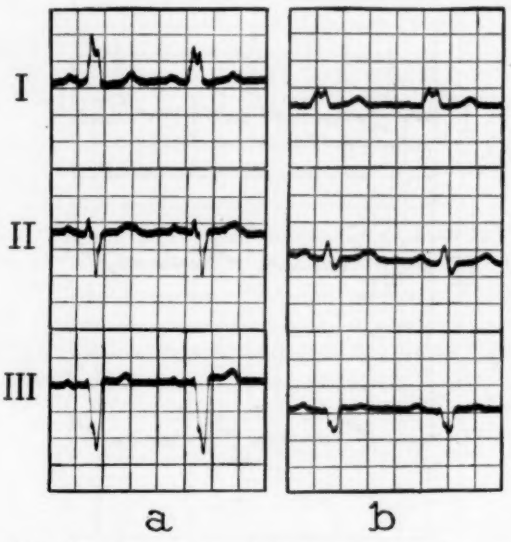

Fig. 3.—Varieties of bundle branch block with discordant graphs showing differences in the amplitude and in the width of the QRS complexes. The T waves in lead I are in the same direction as the major deflection of the QRS complex. Left axis deviation exists in the tracings, but this is not an essential requirement for the diagnosis of bundle branch block with discordant graphs.

nology, it occurred to us that the terms "concordant" and "discordant," originally employed by Lewis,[6] in 1916, to distinguish between the more typical and the less classic forms of electrocardiograms obtained on experimental animals, could be applied adequately to differentiate these two varieties of bundle branch block, the term "concordant" being appended to the classic variety of bundle branch block. The term "intra-

6. Lewis, T.: The Spread of the Excitatory Process in the Vertebrate Heart, Phil. Tr. Roy. Soc., London **207**:221, 1916.

ventricular block" is undesirable because all disturbances of conduction affecting the QRS complex are indeed examples of intraventricular block.

Now in the consideration of any representative series of cases in which there are exhibited conductive disturbances affecting the ventricular complex, it will soon become apparent that the two types just defined (bundle branch block with concordant graphs and bundle branch block with discordant graphs) will not account for all cases in which the QRS interval is prolonged beyond 0.10 second. Thus there is the now

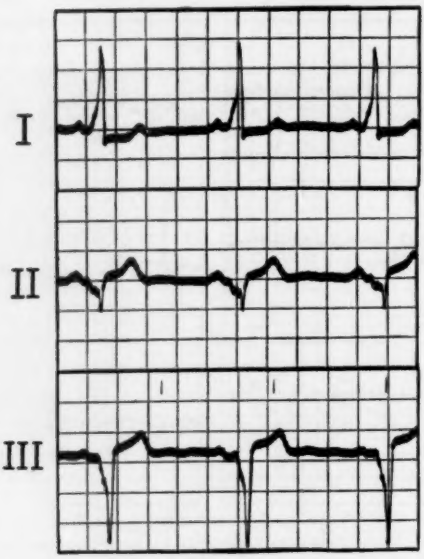

Fig. 4.—This rare type of abnormality is associated with a widening of the QRS complex and an unusually short PR interval.

well recognized, though rare, electrocardiographic pattern described by Wilson,[7] in 1915, in which the ventricular complex resembles that seen in cases of bundle branch block but is associated with a short PR interval (fig. 4).

The remainder of tracings not falling in the aforementioned three categories also possess characteristics which warrant their classification, at least for the time being, in a separate group. We refer specifically

7. Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, Arch. Int. Med. **16**:1008 (Dec.) 1915.

to the electrocardiographic pattern in which the abnormal width of the QRS complex is solely dependent on the S wave, the R component of the ventricular complex being essentially normal. It has been referred to as the pattern for the "rare type" of bundle branch block (which certainly it is not). The picture is so characteristic that it is recognizable at a glance. It is best seen in lead I, and usually also in lead II. It is in a sense the mirror image of the type of prolonged QRS pattern associated with the short PR interval, for whereas the R wave is widened at the expense of the PR interval in the latter, the S wave is widened

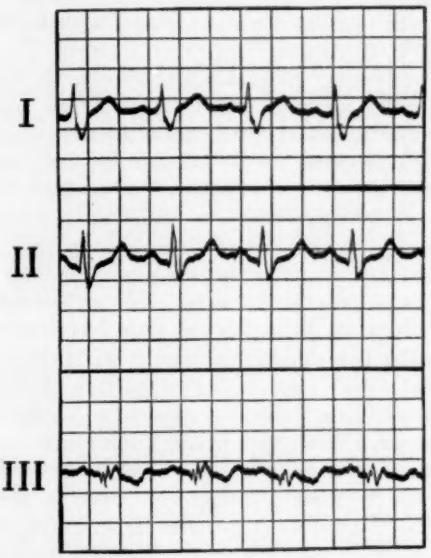

Fig. 5.—Ventricular conduction disturbance with wide S wave pattern. The configuration of this pattern is remarkably uniformly maintained in leads I and II, while lead III shows considerable variation.

at the expense of the RT interval in the former. The differences in the electrocardiograms under discussion are clearly shown in figure 5.

Throughout the literature dealing with bundle branch conduction patterns the last-named group has, in all but a few instances, been indiscriminately considered along with the patterns for the better known conduction defects affecting the ventricular complex and has been regarded by most writers, moreover, as having the same clinical significance as the pattern for bundle branch block in its conventional form.

One of the primary considerations motivating our present survey is an attempt to determine the fate of persons who possess this electro-

cardiographic pattern and to compare it, on the one hand, with that of persons whose electrocardiograms conform to the pattern for the more conventional type of bundle branch lesions and, on the other, with predictions of so-called normal life expectancy as a control.

As far back as 1925, Oppenheimer, Rothschild and Mann [8] commented on this type of electrocardiogram and intimated a relative benignity in the clinical course of patients exhibiting it; subsequently, Von Deesten and Dolganos,[9] as well as Wood, Jeffers and Wolferth,[10] also indicated in follow-up studies that an electrocardiographic pattern of this type often occurred in the absence of other evidence of organic heart disease, lending support, therefore, to a viewpoint diametrically opposed to that which has been current regarding disturbances of conduction affecting the ventricular complex in general.

The urgency for further information relative to the clinical significance of the electrocardiographic pattern is, therefore, apparent. Certain theoretic considerations relative to the interesting phenomenon will be discussed in a subsequent publication, but for the present we shall accept it as indicating a form of disturbance of conduction and confine ourselves to the practical significance of this type of electrocardiogram as it is encountered in the practice of clinical cardiology.

It is surprising that no special nomenclature has been employed in the description of this pattern. In so far as it is characteristic at least in its electrocardiographic configuration (and admitting the undesirability of introducing new descriptive terms when so many are already in use) we feel that it does deserve discrimination in its description. We propose to designate this electrocardiographic pattern simply as "the wide S wave pattern," which is all that it is in reality (recognizing it as a suggestive indication of a disturbance of conduction affecting the ventricular complex of the electrocardiogram), much in the same sense as one speaks of a "lengthened Q_3 pattern" (recognizing this as a suggestive relic of a myocardial infarct involving the posterior basal portion of the left ventricle).

MATERIAL AND METHODS OF EVALUATING DATA

A follow-up study was conducted on all patients examined at the Mayo Clinic between Jan. 1, 1915 and Dec. 31, 1934, inclusive, and on some patients examined in 1935 presenting the various forms of conduction disturbances as defined by us

8. Oppenheimer, B. S.; Rothschild, M. A., and Mann, H.: Cardiographic Differentiation of a Sub-Group of Intra-Ventricular Block with Observations on the Prognosis, J. Clin. Investigation **1**:592, 1925.

9. Von Deesten, H. T., and Dolganos, M.: Atypical Bundle Branch Block with a Favorable Prognosis, Am. J. M. Sc. **188**:231, 1934.

10. Wood, F. C.; Jeffers, W. A., and Wolferth, C. C.: Follow-Up Study of Sixty-Four Patients with a Right Bundle Branch Conduction Defect, Am. Heart J. **10**:1056, 1935.

under the terms bundle branch block with concordant graphs, bundle branch block with discordant graphs and the wide S wave pattern. Those whose records did not contain the necessary follow-up data were traced by letter, and accordingly it was possible to determine the condition of health of 1,611 patients. In a certain number of instances, however, while the information indicated that the patient concerned had died, the date of his demise was not definitely stated, and such cases were discarded in the study referring to life expectancy, leaving 1,476 cases for the computation of data on life expectancy.

According to the criteria for classification already defined, these 1,611 cases were distributed as follows: bundle branch block with concordant graphs, 756 cases (of which 23 were examples of right bundle branch block and 733 of left bundle branch block); bundle branch block with discordant graphs, 363 cases, and the wide S wave pattern, 492 cases.

In the analysis of our material we have deviated somewhat from the method employed in most follow-up studies, as reported in the literature. In many such studies, for example, it has been customary to consider only the patients who have died, to determine the average duration of life of those patients and to base conclusions regarding the mortality of the condition studied on these determinations. There is an actuarial objection to this procedure, based on the fact that this average figure obviously does not represent the average duration of life for the particular lesion under consideration in so far as some patients belonging to the group studied still are living and the duration of life of the person still alive is entirely unknown. Yet the reader is at least tempted to conclude (and usually does) that the average duration, so stated, will apply to any group of patients with a similar lesion. If, on the other hand, the investigator were to continue his follow-up study on a group of patients (sufficiently large to allow for statistical accuracy) until they had all died, then only would the average duration of life for that lesion be represented by such a figure. This, of course, is hardly possible. There is an objection also on the ground that the average duration of life, even were it accurately determined, would not necessarily supply the information which would be of assistance in determining the prognosis for the individual patient.

As the analysis of our data is intimately concerned with the question of life expectancy and prognosis, we resorted through the assistance of the department of biometry and medical statistics of the Mayo Clinic to the method employed in actuarial practice. This method is governed by mathematical laws which allowed computations of the desired data even though a considerable number of the patients falling within the scope of our study were still living at the time the investigation was conducted.

ETIOLOGIC FACTORS

Sex Distribution.—In keeping with the incidence of coronary disease (which is the most common etiologic factor concerned in disturbances of conduction of all kinds), table 1 shows a marked preponderance of males over females in all groups studied. This is particularly noticeable in the group with the wide S wave pattern, a fact which may be of importance in the consideration of the genesis of the lesion associated with this pattern.

Age Distribution.—Table 1 also indicates the distribution by age in the three groups. It will be seen that all types of conduction disturbances affecting the ventricular complex are more common after middle

life (especially between the ages of 50 and 70). In fact, the average age at the time of the diagnosis of the lesion is strikingly similar in the three groups: 58.6 in the case of bundle branch block with concordant graphs, 58.3 in the case of bundle branch block with discordant graphs and 59.3 in the case of the wide S wave pattern.

Associated Clinicopathologic Findings.—Our study confirmed the observation of others that by far the majority of bundle branch lesions result from changes incidental to coronary disease, independently or in association with hypertension. When rheumatic heart disease plays any part in its production, bundle branch block with concordant graphs often assumes the form of right bundle branch block. This is in keeping with the histopathologic studies of Yater. Of the entire series of 1,611

TABLE 1.—*Age and Sex Distribution*

	Concordant Bundle Branch Block		Discordant Bundle Branch Block		Wide S Wave Pattern	
Age at Diagnosis, Years	Number	Per Cent	Number	Per Cent	Number	Per Cent
0- 9	..	...	..	...	2	0.4
10-19	5	0.7	2	0.6	2	0.4
20-29	11	1.5	8	2.2	7	1.4
30-39	29	3.8	13	3.6	19	3.9
40-49	87	11.5	55	15.2	56	11.4
50-59	245	32.4	103	28.4	139	28.3
60-69	274	36.2	124	34.2	182	37.0
70-79	93	12.3	50	13.8	76	15.4
80-89	12	1.6	8	2.2	9	1.8
Total	756	100	363	100	492	100
Youngest	10 years		15 years		9 years	
Oldest	88 years		84 years		88 years	
Average age	58.6 years		58.3 years		59.3 years	
Males	508	67	259	71	395	80
Females	248	33	104	29	97	20
Total	756	100	363	100	492	100

patients, coronary and hypertensive heart disease was considered the etiologic factor in 259 (34 per cent) of the 756 patients with bundle branch block with concordant graphs, in 90 (25 per cent) of the 363 patients with bundle branch block with discordant graphs and in 92 (19 per cent) of the 492 patients with the wide S wave pattern. Coronary sclerosis was regarded as the cause in 296 (39 per cent), 142 (39 per cent) and 141 (29 per cent), respectively, and hypertension alone was considered the etiologic factor in 98 (13 per cent), 41 (11 per cent) and 53 (11 per cent), respectively. Otherwise stated, coronary disease and hypertension, either separately or in association with one another, were stated as the etiologic factor in 86 per cent of patients with bundle branch block with concordant graphs, in 75 per cent of patients with bundle branch block with discordant graphs and in 58 per cent of patients with the wide S wave pattern.

Rheumatic heart disease was present in 85 patients (11 per cent) with bundle branch block with concordant graphs, in 33 (9 per cent) with bundle branch block with discordant graphs and in 44 (9 per cent) with the wide S wave pattern. In the last-named group mitral disease predominated (25 of the 44 patients, while 3 additional ones had mitral stenosis in association with aortic disease), whereas in the other two groups taken together aortic disease predominated over mitral disease in the proportion of 64 to 32 patients. There were 22 patients (3 per cent) with syphilitic aortitis in the group with bundle branch block with concordant graphs, 7 (2 per cent) in the group with bundle branch block with discordant graphs and 6 (1 per cent) in the group with the wide S wave pattern. The remainder comprised persons with congenital heart disease and various miscellaneous etiologic factors.

SURVIVAL CURVES

In figure 6 are shown the survival curves calculated for the three groups showing types of disturbance of conduction and for the normal population of similar sex and age.[11] Each curve gives the expected number of persons out of 100 who will be living for each consecutive year after the diagnosis is made. It is seen that the survival curve for each of the groups of patients is considerably below that for the normal population and that the lowest level of survivors is found in the group with bundle branch block with concordant graphs, the next lowest in that with bundle branch block with discordant graphs and the highest in that with the wide S wave pattern. The steepest descent in the survival curve, indicating a high death rate, is seen in the first year. This applies to all of the three groups of defects of conduction studied. After the first year the curves tend to level off. One year after the diagnosis has been made, 80 per cent of patients with the wide S wave pattern, 67 per cent of those with bundle branch block with discordant graphs and 57 per cent of those with bundle branch block with concordant graphs are living. After the first year, the group with the wide S wave pattern maintains practically a constant death rate from year to year which is but slightly greater than that for the normal population. After ten years 38 per cent of the patients in this group are still alive, as compared with 65 per cent in a normal population of the same age, the discrepancy in the number of those surviving among the group with the wide S wave

11. The methods of calculating the mortality and survival rates followed the regular principles used in actuarial practice (for example, "Construction of Mortality Tables from the Records of Insured Lives," New York, The Actuarial Society of America, 1922), and the calculations for this study were made in the division of biometry and medical statistics of the Mayo Clinic.

pattern as compared with those among the normal population being accounted for mainly by the high mortality rates in the first year after the discovery of the defect of conduction.

In the groups with bundle branch block of the concordant and of the discordant type, the annual death rate is greater than that for the group with the wide S wave pattern not only during the first year but also in succeeding years, so that only 16 and 26 per cent of the respective original groups were alive ten years after the diagnosis had been established, figures which reflect a more serious prognosis for these groups than for the group with the wide S wave pattern. One difference to be noted between the two groups is that whereas the survival curve for the group with bundle branch block with discordant graphs after

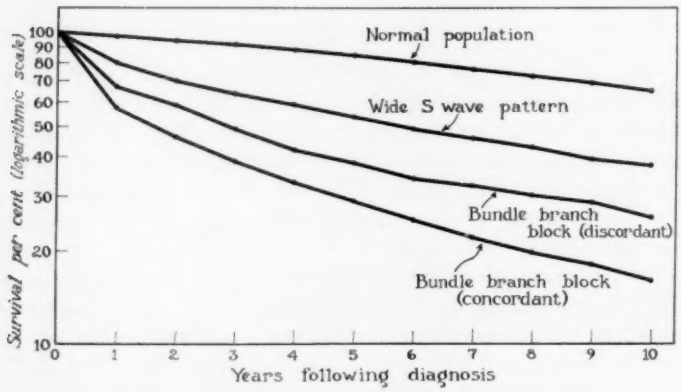

Fig. 6.—Survival curves of groups of patients with bundle branch block with concordant graphs, bundle branch block with discordant graphs and the wide S wave pattern as compared with that of a normal population of the same age and sex.

about the fifth year approximates normal, that for the group with bundle branch block with concordant graphs continues to show a higher mortality, as indicated by the greater steepness of the corresponding curve.

MORTALITY

In tables 2 and 3 the mortality experience is presented in the form of annual death rates for various years after the diagnosis was made. In table 2 it is seen that in the first year the mortality rate for bundle branch block with concordant graphs is 43 per cent, for bundle branch block with discordant graphs 33 per cent and for the wide S wave pattern 20 per cent. These are to be contrasted with a death rate of

about 3 per cent for a normal white male population of similar age. The annual death rate for the persons who survive one year is seen to be 20 per cent for those with bundle branch block with concordant graphs, 13 per cent for those with bundle branch block with discordant graphs and 12 per cent for those with the wide S wave pattern. The death rates themselves are not so great after the first year following diagnosis as they are for the first year, but the death rates for the three types have about the same ratio to one another as for the first year after diagnosis. After the fourth year it is seen that the annual rates for the

TABLE 2.—*Annual Death Rate from All Causes, Per Cent; Comparison of Patients with Conductive Defects and Normal Population*

Years After Diagnosis	Annual Death Rate, Per Cent			
	Concordant Bundle Branch Block	Discordant Bundle Branch Block	Wide S Wave Pattern	Normal Population
0- 1	42.5	32.5	19.9	2.6
1- 2	19.9	13.0	12.2	2.8
2- 5	14.7	13.9	8.6	3.3
5-10	11.3	7.5	7.3	4.6

TABLE 3.—*Annual Death Rate from Cardiac Causes, Per Cent; Comparison of Patients with Conductive Defects and Normal Population*

Years After Diagnosis	Annual Death Rate, Per Cent Conductive Defects *			
	Concordant Bundle Branch Block	Discordant Bundle Branch Block	Wide S Wave Pattern	Normal Population
0- 1	41.0	30.7	17.8	0.9
1- 2	17.6	10.5	9.7	1.0
2- 5	11.8	11.0	5.5	1.1
5-10	7.0	3.0	2.8	1.2

* The death rate from cardiac causes in the groups of patients was obtained by correcting the rate from all causes as observed (table 2) by rates for causes other than cardiac in the general population.

groups with the wide S wave pattern and bundle branch block with discordant graphs are both about 7 per cent, whereas the group with bundle branch block with concordant graphs has an annual death rate of about 11 per cent, as contrasted with a rate of about 5 per cent for the normal population.

In table 3 is made the same sort of comparison as in table 2, except that the rates are confined to deaths from cardiac causes. The contrast between the mortality rates of patients with disturbances of conduction and those of the normal population is naturally much greater when the death rates from cardiac causes alone rather than rates from all causes are considered, but the general comparisons are similar to what was shown in table 2.

CONDITION OF THE PATIENT IN THE SERIES AT THE LAST REPORT

Table 4 summarizes the facts relative to the condition of all patients at the time of the last report. The prognostic trend inherent in this table coincides with the facts revealed by the life expectancy curves already discussed. The column referring to the deaths due to unknown causes requires some comment. Instances in which the death was presumably primarily from a cardiac cause but in which this fact is not so stated in the follow-up information are included in this group. The clinical findings at the time of the last examination would tend to indicate that the percentage of deaths due to cardiac causes in this group is fairly high. In so far as this is applicable to all three types of conductive disturbance studied, the true facts remain undistorted from the general standpoint of life expectancy and prognosis.

TABLE 4.—*Condition at Last Report*

	Concordant Bundle Branch Block		Discordant Bundle Branch Block		Wide S Wave Pattern	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Living, well	47	6.2	46	12.7	125	25.4
Living, well with rest	48	6.3	31	8.5	46	9.3
Living, not well	14	1.9	9	2.5	11	2.2
Living, condition unknown	2	0.3	2	0.6	2	0.4
Dead, cause cardiac	334	44.2	122	33.6	95	19.3
Dead, cause other than cardiac	57	7.5	48	13.2	85	17.3
Dead, cause unknown	254	33.6	105	28.9	128	26.0
Total	756	100.0	363	100.0	492	100.0

COMMENT

The discovery of a conductive defect of any type is to be regarded, until proved otherwise, as indicative of a lesion which has inflicted damage not only on the bundle of His or its ramifications but also on the myocardium itself. The high incidence of clinically demonstrable organic heart disease among persons exhibiting one or another electrocardiographic pattern indicative of a conductive defect soon fostered the belief that such defects were invariably of serious prognostic significance. Indeed, when one considers that all pathologic lesions capable of inflicting myocardial damage (be it the result of arteriosclerosis, of an inflammatory process such as rheumatic disease or syphilis or of hypertension) are inherently progressive in nature, there seems to be good justification for such a belief.

The one factor that was not appreciated for a long time was the extent to which the cardiovascular apparatus is capable of readjusting itself to processes, even though their natural tendency may be toward progression. The eventual means of readjustment lies in the process of revascularization of regions deprived of their original blood supply.

In this connection it is to be recalled that the conductive tissues are more highly specialized than the rest of the myocardium, so that restoration of function after injury is less likely to occur in the former than in the latter. One needs only to be reminded of the evolution of the present day attitude toward the clinical event of acute coronary occlusion. Not much more than two decades ago it was universally believed that the prolongation of life was incompatible with such an occurrence. Now it is known that this is far from the truth. And indeed are not conductive disturbances in the vast majority of cases simply another manifestation of the same process which so frequently culminates in acute myocardial infarction, namely, coronary sclerosis? Yater went so far as to suggest that the damage to the conductive system, as encountered in rheumatic heart disease, is the result of a similar interference with its blood supply.

In short, it has become clear that the prognosis of heart disease is determined by the progress of the underlying pathologic process (against such readjustments as the coronary system can make) rather than by the mere evidence demonstrable by instrumental means that a pathologic process actually exists. Moreover, in the evaluation of instrumental evidence of heart disease, due allowance must be made for the sampling among persons who are submitted for electrocardiographic study. The files of any electrocardiographic laboratory are liable to be replete with tracings of patients in whom cardiac disease is either manifest or suspected.

In keeping with this revised viewpoint relative to the life history of coronary disease and with the wider application of the electrocardiogram in diagnosis, it has become apparent that among patients with conductive disturbances, regardless of the type, there are instances (as there are instances of patients who have had a coronary occlusion) in which the clinical course proves relatively favorable.

Referring mostly to patients with what we include under the terms bundle branch block with concordant graphs and bundle branch block with discordant graphs,[12] several investigators have indicated that while the mortality seems to be high during the first year after discovery of the lesion, a remarkable diminution in the mortality rate occurs among those patients who survive this period. Referring particularly to those with the wide S wave pattern, others [13] have remarked on the frequent

12. Sampson, J. J., and Nagle, O. E.: The Prognosis of Bundle Branch Block and Other Intraventricular Conduction System Lesions, Am. J. M. Sc. **191**:88, 1936. Bishop, L. F., Jr., and Carden, G. A., Jr.: The Prognosis of Bundle Branch Block, Am. Heart J. **17**:275, 1939. Kaplan, L. G., and Katz, L. H.: Prognosis of Intraventricular Block, ibid. **18**:145, 1939.

13. Oppenheimer, Rothschild and Mann.[8] Von Deesten and Dolganos.[9] Wood, Jeffers and Wolferth.[10]

existence of this type of electrocardiogram among patients who exhibit no clinical evidence of organic heart disease at all and who progress favorably during the period (often many years) over which they are under observation.

In the studies cited in the literature the number of patients reported on was relatively small in each case, so that the need for testing the accuracy of these observations is therefore important. This we feel we have accomplished in the present study.

We believe, further, that on the basis of this study there is good justification for the subdivision into the different varieties, as defined by us, of conductive disturbances affecting the ventricular complex. They differ one from the other not only in their essential electrocardiographic configuration but also in their clinical course. It is true that between bundle branch block with concordant graphs and bundle branch block with discordant graphs, as defined by us, there is close parallelism throughout, as has been noted before;[14] yet when the life expectancy curves are followed, there is sufficient difference to group the two disturbances separately.

It has long been known that patients with significant negativity of the T wave have, on the whole, a less favorable prognosis than those with the same pathologic lesion not attended by changes in the T wave. It would seem that this electrocardiographic law applies equally well when patients with two types of bundle branch block (that with concordant and that with discordant graphs) are compared with each other. There certainly is ample justification, on the basis of the clinical course alone, for placing patients with the wide S wave pattern in a separate group.

SUMMARY

Conductive disturbances affecting the ventricular complex have been variously classified and named by various authors. In the light of recent histopathologic studies in cases in which the electrocardiogram showed bundle branch defects and on the basis of the clinical behavior of patients who harbor these lesions, we suggest that conductive defects affecting the QRS complex be classified as follows: (1) bundle branch block with concordant graphs; (2) bundle branch block with discordant graphs including those cases in which the patterns resemble the electrocardiograms in the first class but without directional change in the T wave and without correlating axis deviation; (3) bundle branch block associated with the wide S wave pattern, which accounts for the increased width of the QRS complex, and (4) the type of bundle branch block

14. White, P. D., and Viko, L. E.: Clinical Observations on Heart Block, Am. J. M. Sc. **165**:659, 1923. Graybiel, A., and Sprague, H. B.: Bundle Branch Block: An Analysis of Three Hundred and Ninety-Five Cases, ibid. **185**:395, 1933.

associated with a short PR interval (in reality a wide R wave pattern). The last is the rarest form of conduction disturbance affecting the QRS complex.

The terms complete and incomplete bundle branch block are no longer tenable so far as the electrocardiogram has been shown incapable of reflecting the extent of interruption of the bundle branches. It has also been shown that lesions affecting the conductive system similar to those causing the electrocardiographic pattern known to indicate complete bundle branch block with concordant graphs need not be associated with increased amplitude of the QRS complex or with slurring of the complexes nor need the pattern which they produce primarily conform to the classic levocardiogram or dextrocardiogram. The first class includes all cases in which the QRS spread measures more than 0.10 second, regardless of the amplitude of the complex or of slurring, in which the T waves in leads I and III are directed opposite to the main deflection of the QRS complex. The disturbance may assume the form of left or right bundle branch block, depending on which bundle is predominantly affected. The latter is by far the rarer of the two, and its occurrence depends in many cases on the existence of rheumatic heart disease, while hypertension and coronary disease most frequently account for the former.

In a follow-up study of a series of patients comprising 756 with bundle branch block of the concordant variety, 363 with bundle branch block of the discordant variety and 492 with the wide S wave pattern, it is shown by computation of life expectancy curves and of death rates (by actuarial methods) that the life histories of patients harboring these lesions differ one from the other. In the case of the last-named group, namely, that with the S wave pattern, the course is by far the most favorable. The highest mortality occurs during the first year after the discovery of the lesion (20 per cent). After this the annual death rate drops so that the life expectancy curve tends to parallel that of the normal population. After the S wave pattern has existed for ten years, more than a third of the patients are still alive. This is especially significant when it is remembered that the average age of the patients at the time the lesion is discovered is almost 60 years.

In the case of the group with bundle branch block with concordant graphs the highest mortality rate is also seen in the first year after the diagnosis is made, and this is the highest rate found in all the groups studied (43 per cent). As in the case of the patients with wide S wave pattern, the mortality rate drops in the succeeding years, but throughout the remaining period of study the life expectancy curve continues to drop faster than that for the normal population, so that only about 16 per cent of patients are alive ten years after the original diagnosis. Patients whose electrocardiograms show bundle branch block of the dis-

cordant type as defined by us follow a course intermediate between those of the two groups mentioned. The life expectancy curve in the first few years parallels closely that for the group with bundle branch block with concordant graphs, but after the fifth year the annual death rate drops (as compared with the first five years), so that the curve parallels that for the group with the wide S wave pattern as well as that for the normal population. In the case of the group with bundle branch block with discordant graphs 26 per cent of patients are still living ten years after the diagnosis.

Our study supports the contention that conductive defects affecting the ventricular complex have on the whole a better prognosis than was indicated by earlier studies and emphasizes the fact that prognostication must not depend on the consideration of the electrocardiographic pattern alone but that consideration must be given to the clinical condition of the patient and the functional status of the heart. The study clearly indicates that what we have termed the wide S wave pattern deserves separate classification not only on the basis of its electrocardiographic configuration but especially on the basis of the life history of patients who harbor such a disturbance.

LIFE EXPECTANCY IN CONDUCTIVE DISTURBANCES AFFECTING THE VENTRICULAR COMPLEX OF THE ELECTROCARDIOGRAM

II. SPECIAL CONSIDERATION OF BUNDLE BRANCH BLOCK WITH CONCORDANT GRAPHS AND WITH DISCORDANT GRAPHS

RICHARD REESER JR., M.D.
Fellow in Medicine, the Mayo Foundation

FREDRICK A. WILLIUS, M.D.
AND
THOMAS J. DRY, M.B.
ROCHESTER, MINN.

The reasons for the reclassification of bundle branch lesions, as indicated elsewhere,[1] center chiefly around the histopathologic studies of Yater and his co-workers[2] and of Mahaim,[3] who have indicated, first, that the fibrotic changes in the conduction system which are responsible for the electrocardiographic pattern of bundle branch block are usually bilateral, though one branch is liable to show destructive effects to a more advanced degree than the other; second, that when the brunt of the destructive changes is borne by the left branch, the etiologic factor concerned is usually coronary disease or hypertension, whereas the reverse is true most generally when the heart is the seat of a chronic rheumatic lesion; third, that the amplitude of the ventricular complexes

From the Section on Cardiology, the Mayo Clinic (Drs. Willius and Dry).

1. Willius, F. A.; Dry, T. J., and Reeser, R., Jr.: Life Expectancy in Conductive Disturbances Affecting the Ventricular Complex of the Electrocardiogram: I. General Considerations of Bundle Branch Block with Concordant and with Discordant Graphs, and the Wide S Wave Pattern, Based on 1,611 Cases, Arch. Int. Med., this issue, p. 1008.

2. Yater, W. M.; Cornell, V. H., and Claytor, T.: Auriculoventricular Heart Block Due to Bilateral Bundle Branch Lesions: Review of the Literature and Report of Three Cases with Detailed Histopathologic Studies, Arch. Int. Med. **57**:132 (Jan.) 1936. Yater, W. M.: Pathogenesis of Bundle Branch Block: Review of the Literature; Report of Sixteen Cases with Necropsy and of Six Cases with Detailed Histologic Study of the Conduction Systems, ibid. **62**:1 (July) 1938.

3. Mahaim, I.: Les maladies organiques du faisceau de His-Tawara: Les syndromes coronaires. L'endocardite septale. L'infarctus septal (étude clinique et anatomique), Paris, Masson & Cie, 1931; Nouvelles recherches sur les lésions du faisceau de His-Tawara (deuxième mémoire); le bloc de branche gauche et sa pathogénie; la septite mitrale, Ann. de méd. **38**:185, 1935.

does not seem, according to Yater's observations, to be entirely dependent on the state of the bundle branches as these are found in serial sectional studies; fourth, that slurring and notching of the ventricular complexes are not a necessary accompaniment of extreme bundle branch lesions, and, fifth, that the actual width of the QRS complexes, which varied from 0.12 to 0.16 second in the cases studied by Yater, is not dependent on the degree of destruction of the bundle branches. In 6 cases of bundle branch block reported by Yater (3 examples of predominantly right-sided lesions and 3 of predominantly left-sided lesions) the T waves were directed opposite to the main deflection of the QRS complex in leads I and III in all cases. In short, a lesion similar to that which has been regarded as responsible for the classic dextrocardiogram and the classic levocardiogram may at times result in more attenuated patterns as reflected by the electrocardiogram. Certainly the completeness or the incompleteness of the degree to which one or the other bundle has been destroyed does not seem to be reflected by the electrocardiogram and certainly not by the width of the QRS complex, as had previously been assumed, mostly on the basis of animal experiments.

We have, therefore, proposed to discard the terms "complete" and "incomplete" and include under the term "bundle branch block" with concordant graphs all cases in which the QRS complex measures more than 0.10 second, regardless of the amplitude of the ventricular complex or of slurring and of notching, and in which the T waves are directed opposite to the main deflection of the QRS complexes in leads I and III. Recognizing the universal bilaterality of these lesions, we accept the terms "right" and "left," as applied to bundle branch block as defined, to indicate more advanced damage to one or the other bundle branch.

When we exclude those electrocardiographic patterns which conform to the wide S wave pattern and the rare examples of bundle branch block associated with a short PR interval, the remainder of electrocardiograms in which the QRS interval is prolonged beyond 0.10 second differ from those showing bundle branch block with concordant graphs as defined in the preceding paragraph only in so far as the T waves are not opposite to the main deflection of the QRS complexes and in so far as they are not associated necessarily with correlating axis deviation. Cases in which these patterns, representing a less classic electrocardiographic pattern, appear we propose to designate bundle branch block with discordant graphs. It is to be stressed that hearts in cases in which electrocardiograms conformed to this pattern have thus far not been submitted to serial sectional studies.

A study of the life expectancy of patients who harbor lesions corresponding to bundle branch block with concordant graphs (right and

left) and of those with bundle branch block with discordant graphs has revealed a fairly close parallelism; yet as patients were followed from year to year after the discovery of the electrocardiographic abnormality, the latter group showed a more favorable course on the whole than the former, and for this reason, in addition to the electrocardiographic differences already enumerated, it would seem wise to separate the lesions from each other—at least until more information regarding the morphologic changes involved in their production becomes available.

ETIOLOGIC FACTORS

Age Incidence.—The ages varied from 10 to 88 years in the group with bundle branch block with concordant graphs and from 15 to 84 years in that with bundle branch block with discordant graphs, the average age at the time of diagnosis being 58.6 and 58.3 years, respectively, as compared with 59.3 years in the case of the group associated with the wide S wave pattern.

Sex Incidence.—Males predominated over females in the proportion of 508 to 248 in the case of bundle branch block with concordant curves and of 259 to 104 in the case of bundle branch block with discordant graphs.

Coronary Sclerosis and Hypertension.—Either independently or in association with each other, these conditions were regarded as the etiologic factor in 653 of the 756 cases (86 per cent) of bundle branch block with concordant graphs and in 273 of the 363 cases (75 per cent) of bundle branch block with discordant curves.

Rheumatic Heart Disease.—The diagnosis of rheumatic lesions was made in 85 cases of bundle branch block with concordant graphs and in 33 cases of bundle branch block with discordant graphs. The distribution was as follows: (1) right bundle branch block, 9 cases (with mitral stenosis in all); (2) left bundle branch block, 76 cases (with aortic disease in 50, mitral disease in 13 and both aortic and mitral disease in 12; in an additional case the condition was designated as rheumatic heart disease without further qualification), and (3) bundle branch block with discordant graphs, 33 cases. Of these, aortic disease was present in 14 and mitral disease in 10, and in 9 both aortic and mitral disease existed.

In comparison, it might be added that rheumatic lesions were associated in 44 instances with the wide S wave pattern, of which 25 were examples of mitral disease, 3 of mitral stenosis in association with aortic disease and 13 of aortic disease. It is to be noted that the incidence of aortic and mitral disease is exactly reversed in the last-named group, as compared with the other two groups.

Syphilitic Aortitis with Aortic Insufficiency.—This condition occurred in 22 patients of the group with left bundle branch block with concordant graphs (and in none of the group with right bundle branch block); 7 patients with bundle branch block of the discordant variety had syphilitic aortic disease.

Congenital Heart Disease.—This condition was diagnosed in 1 case of right bundle branch block, in 2 cases of left bundle branch block (both concordant) and in 3 cases of bundle branch block with discordant curves. In the remaining cases, a variety of conditions existed which were not regarded as helpful in the consideration of causal factors.

THE LIFE HISTORY OF PATIENTS WITH BUNDLE BRANCH BLOCK OF THE CONCORDANT AND THE DISCORDANT TYPE

The main facts relative to the fate of patients who harbor these two types of conductive disturbance, which have been considered in detail elsewhere, may be recapitulated briefly as follows: Within the first year after discovery of the disturbance there is a heavy mortality in both groups (43 and 33 per cent, respectively). In 63 per cent of the patients with bundle branch block with concordant graphs and 56 per cent of the patients with bundle branch block with discordant graphs, death is attributable directly to cardiac causes. During the years which follow, the death rates in the two groups drop considerably and for four or five years they parallel each other closely. By the sixth year, however, the death rate in the group with discordant graphs tends to parallel more closely the life expectancy curve of both the group with the wide S wave pattern and the normal population, whereas the group with bundle branch block shows a life expectancy curve which continues to drop faster than those for the normal population and for the other two groups. At the end of ten years 60 patients with concordant graphs, 37 patients with discordant graphs and 62 patients with the wide S wave pattern are still alive. After these figures are adjusted to a comparable basis by use of the life table analysis, the percentage of patients expected to live ten or more years would be 16, 26 and 38 respectively. The corresponding figure as obtained from a general life table population is 65 per cent.

Patients Who Had Died by the End of the First Year.—In the group with discordant graphs 290 of the original 756 patients used in the computation of the life expectancy tables had died by the end of the first year after the discovery of the conduction defect. Since this represents the heaviest mortality during the entire period covering the survey, we analyzed the data relative to these patients, as these data would be expected to reflect the factors responsible for the high death rate. Of the 290 patients death was attributed to cardiac causes in 183 (63 per

cent) and to other causes in 27 (9 per cent). In 80 patients the cause could not be defined with certainty, though in all probability their number included several deaths due to cardiac disease.

Cardiac enlargement noted by clinical or roentgenologic methods or both was thought to be present in 241 patients (83 per cent); the number dying as a result of cardiac causes showed a particularly high percentage of cardiac enlargement (166 of 183 patients, or 91 per cent). Angina pectoris or congestive heart failure, either individually or in association with each other, occurred in 183 patients (63 per cent). The diagnosis of acute coronary occlusion was made in 22 of the number of patients dying during the first year of observation.

In the group with discordant curves evidence of gross cardiac disease was equally obvious, the number of patients dying of cardiac causes being 60 (56 per cent) of the 108 patients in this group. Twenty-one patients died of causes apparently unrelated to their cardiac condition, and in 27 instances the cause of death was unknown or uncertain.

Cardiac enlargement was noted in 81 patients (75 per cent); angina pectoris and congestive heart failure occurred either separately or in association with each other in 60 patients (56 per cent). The condition of 9 patients belonging to this group was diagnosed as acute coronary occlusion.

Patients Who Were Living Ten Years or More After the Original Diagnosis.—In the group with concordant bundle branch block there were 60 and in the group with discordant bundle branch block there were 37 patients who were living ten years or more after the recognition of their electrocardiographic abnormality. An analysis of the clinical findings made at the time of the discovery of the conduction disturbance revealed the following facts: A systolic blood pressure of 170 mm. of mercury or more and/or a diastolic pressure of 100 mm. of mercury or more was noted in 22 of the 60 patients in the former group and in 10 of the 37 patients in the latter group. Cardiac enlargement was thought to be present in 36 of the former group and in 12 of the latter. A diagnosis of angina pectoris was recorded in 10 cases of concordant bundle branch block and in 3 cases of discordant bundle branch block. Congestive heart failure occurred in 1 patient belonging to the former group and in 3 patients belonging to the latter group. The relative absence of symptoms in many of these patients at the time of their original diagnosis is indicated by the fact that in the cases of only 8 patients with concordant curves and of 15 with discordant curves (to be contrasted with 42 of the 62 patients with the wide S wave pattern) was the diagnosis of coronary disease made entirely on the electrocardiographic findings.

The Clinical Status of These Patients at the Time of the Last Inquiry.—Of the 60 patients with bundle branch block with concordant curves

who lived for ten years or longer, 22 had died at the time of the last report and 38 were living. Twenty-one of the 38 patients regarded themselves as being in good health, 15 were progressing favorably with restrictions and 2 regarded their health as poor in spite of restrictions. Of the 37 patients with bundle branch block of the discordant variety who lived for ten years or longer, 10 had died and 27 were living. Sixteen of the 27 patients were well, 8 were well under a restricted program and 2 were not getting along well in spite of restrictions. In 1 instance the clinical condition of the patient could not be ascertained.

THE GENERAL INCIDENCE OF CARDIAC SYMPTOMS IN THE TWO GROUPS AS A WHOLE

There are certain objections on statistical grounds to the consideration of the functional status of the heart in a heterogeneous group of patients of different ages seen over a number of years and followed for varying periods. But in so far as it was intended to draw comparisons between these groups and groups with other types of conductive disturbances (which would be subject to similar discrepancies), the incidence of congestive heart failure and of angina pectoris was computed for each group studied. It was felt that lesser degrees of coronary insufficiency and of myocardial degeneration would be extremely difficult to evaluate from the histories. Patients with paroxysmal nocturnal dyspnea were regarded as having early congestive heart failure. In the group with the concordant type of bundle branch block, angina pectoris without congestive heart failure was diagnosed in 125 cases (17 per cent) and congestive heart failure without angina pectoris in 201 cases (27 per cent). When the two conditions were considered together, it was found that in 44 per cent of patients with bundle branch block one or both conditions existed at the time the diagnosis was made. In the group with discordant curves, 48 patients (13 per cent) had angina pectoris without congestive heart failure, 81 patients (22 per cent) had congestive heart failure without angina pectoris and 37 per cent in all had either angina pectoris or congestive failure or both at the time the diagnosis was made. This is to be contrasted with 50 patients (10 per cent) with angina pectoris without congestive failure and 57 patients (12 per cent) with congestive failure without angina pectoris, or 22 per cent with one or both conditions in the group with the wide S wave pattern.

SUMMARY

The facts revealed by the detailed analysis of these types of conductive disturbance affecting the ventricular complex, namely, bundle branch block with concordant and with discordant graphs, as defined by us, emphasize again the desirability for the reclassification of such

lesions. The etiologic background from the standpoint of age and sex incidence, on the one hand, and of associated clinicopathologic findings, on the other, seems to be essentially similar in character in the two types of conduction disturbance. At the same time, the clinical course of patients whose electrocardiogram conforms to the type described as the discordant variety of bundle branch block is somewhat more favorable than is that of patients with the concordant type of bundle branch block.

Evidence of gross cardiac disease manifests itself in a high percentage of cases in the types of conductive disturbance under consideration. Our studies, however, confirm the contention expressed in some of the more recent publications dealing with this subject, that bundle branch lesions are not universally of serious prognostic significance so that in the evaluation of the cardiac status due consideration must be given to clinical data when an electrocardiographic abnormality indicative of a conductive disturbance is found to exist.

LIFE EXPECTANCY IN CONDUCTIVE DISTURBANCES AFFECTING THE VENTRICULAR COMPLEX OF THE ELECTROCARDIOGRAM

III. SPECIAL CONSIDERATION OF THE WIDE S WAVE PATTERN, WITH REPORT OF THREE CASES

THOMAS J. DRY, M.B.

FREDRICK A. WILLIUS, M.D.

AND

RICHARD REESER JR., M.D.

Fellow in Medicine, the Mayo Foundation

ROCHESTER, MINN.

In a previous publication [1] we have indicated that the wide S wave pattern differs from electrocardiograms produced by other forms of bundle branch defects not only in its electrocardiographic configuration but also (and this is of greater moment) in its life history. What adds to the importance of this form is not only its relative benignity but also its relative frequency. It occurred in our material as the second commonest form of conductive disturbance affecting the ventricular complex. The authenticity of its frequent occurrence can be corroborated simply by examining the electrocardiograms which have been reproduced from time to time in reports on bundle branch block already in the literature in which it will be seen repeatedly grouped along with the conventional forms of bundle branch lesions (usually the conventional type of right bundle branch block).

CHARACTERISTICS OF THE WIDE S WAVE PATTERN

The appearance of the electrocardiogram is uniformly striking, and it is seldom necessary to confirm by actual measurement that the extra width of the QRS complex is dependent solely on an S wave, broadly slurred in its most distal segment. This is best illustrated in lead I, though in many instances lead II is practically identical with lead I and

From the Section on Cardiology, the Mayo Clinic (Drs. Dry and Willius).

1. Willius, F. A.; Dry, T. J., and Reeser, R., Jr.: Life Expectancy in Conductive Disturbances Affecting the Ventricular Complex of the Electrocardiogram: I. General Considerations of Bundle Branch Block with Concordant and with Discordant Graphs and the Wide S Wave Pattern, Based on 1,611 Cases, Arch. Int. Med., this issue, p. 1008.

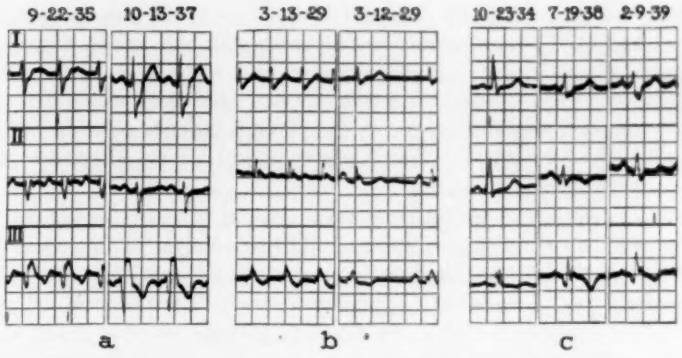

Fig. 1.—*a*, the wide S wave pattern associated with auricular flutter, on Sept. 22, 1935, and the pattern in the same patient, with a normal rhythm, on Oct. 13, 1937, illustrating the constancy in the configuration of the QRS complex, despite an ectopic rhythm. *b*, an example of nodal tachycardia, March 13, 1929. The QRS complex is essentially similar to that on March 12, 1929, when the rhythm was normal. *c*, the effect of acute coronary occlusion on the electrocardiogram of a patient with a wide S wave pattern. The electrocardiogram taken on July 19, 1938 was preceded two weeks by typical coronary occlusion. Note the contour changes in leads II and III, which later disappear.

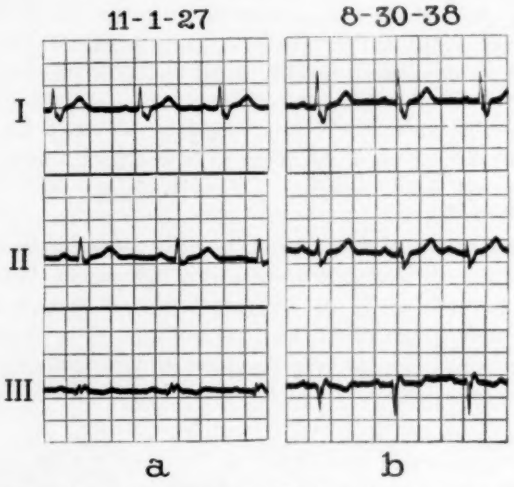

Fig. 2.—Two electrocardiograms recorded about eleven years apart on a patient, now 80 years old, who had no cardiac symptoms.

even lead III may show at times the essential features noted in the preceding sentence. Actually, lead III does not follow a definite pattern. Thus the QRS complex may be diphasic with the initial deflection directed either upward or downward, or the QRS complex may be monophasic. We were unable to disclose any data which would indicate important differences of prognostic significance dependent on the variation described in lead III. The T waves in lead III are inverted in the majority of instances.

The picture described in the preceding paragraph may be associated with any other recognized type of electrocardiographic abnormality. Ectopic rhythms do not alter the fundamental configuration of the QRS complex (fig. 1 *a* and *b*). The amplitude of the R waves in lead I and of the S waves in lead III was noted to increase in some cases with associated hypertension as the patients were followed over a period of years. The contour of changes in the RT segment characteristic of acute coronary thrombosis resemble those seen in cases in which electrocardiograms have a normal QRS width, but the cove-shaped element has its take-off from the upstroke of the S wave rather than from the downstroke of the R wave (fig. 1 *C*). The electrocardiogram may show remarkably few changes over a number of years in certain cases (fig. 2).

THE PROBABLE SIGNIFICANCE OF THE WIDE S WAVE PATTERN

In so far as the wide S wave pattern is associated with an increased width of the QRS complex, it implies the existence either of a lesion interfering with conduction or perhaps of some mechanism resulting in asynchronism in the dynamic events of the two ventricles independent of a conductive disturbance.

A considerable amount of evidence supports the viewpoint that this type of electrocardiogram is the result of a disturbance of conduction affecting the right bundle branch. This evidence may be summarized briefly as follows:

1. The electrocardiographic pattern resembles that obtained in some experimental animals after destruction of the right bundle branch.[2]

2. The time relations of the dynamic events of the two ventricles indicate that with lesions of this kind the left ventricle contracts before the right ventricle. This has been illustrated both clinically and experimentally. Thus, as Wolferth and Margolies[3] have shown, the carotid

2. Roberts, G. H.; Crawford, J. H.; Abramson, D. I., and Cardwell, J. C.: Experimental Bundle-Branch Block in the Cat, Am. Heart J. **7**:505, 1932.

3. Wolferth, C. C., and Margolies, A.: Asynchronism in Contraction of the Ventricles in the So-Called Common Type of Bundle-Branch Block: Its Bearing on the Determination of the Side of the Significant Lesion and on the Mechanism of Split First and Second Heart Sounds, Am. Heart J. **10**:425, 1935.

wave of the phlebogram (indicating contraction of the left ventricle) is inscribed before the right ventricle contracts, as indicated by sound tracings taken simultaneously with the phlebogram and the electrocardiogram. They pointed out that the first heart sound is usually split in cases of this lesion and that the second component of this split sound, which they regarded as indicative of right ventricular contraction, occurs after the inscription of the carotid wave. Braun-Menendez and Solari [4] registered the time relations of the contractions of the two ventricles before and after cutting the right bundle branch in dogs and found that whereas before section of the bundle the two ventricles contracted simultaneously, after section the left ventricle contracted as much as 0.04 second before the right ventricle. Some of the tracings reproduced after section of the right bundle branch closely resemble the wide S wave pattern, as seen in clinical electrocardiograms.

3. Chest leads taken serially across the precordium also indicate that the left ventricle contracts before the right ventricle in cases in which there is an electrocardiogram of the wide S wave pattern. Thus, Wilson and his co-workers [5] were able to show that when the exploring electrode is placed over the region of the right ventricle the upstroke of the R wave occurs relatively late and that when the electrode is placed over the region of the left ventricle the upstroke of the R wave is relatively early, as timed in each case against one of the conventional leads taken synchronously with the chest leads.

We are reminded of one circumstance under which an electrocardiogram indistinguishable from the wide S wave pattern occurs as a temporary event.[6] This circumstance is the early phases of acute pulmonary embolism, when the right ventricle is suddenly subjected to a tremendously increased load, presumably as a result of spasm of the entire pulmonary arteriolar bed. Information is not available as to whether this electrocardiographic change is a fatigue phenomenon (biochemical) or one dependent on asynchronism of the two ventricles (mechanical) or, for that matter, on some other, unknown factor. In the meantime, however, we wish to record that such an electro-

4. Braun-Menendez, E., and Solari, L. A.: Ventricular Asynchronism in Bundle Branch Block, Arch. Int. Med. **63**:830 (May) 1939.

5. Wilson, F. N.; Johnston, F. D.; Hill, I. G. W.; Macleod, A. G., and Barker, P. S.: The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S-Deflections in Lead I, Am. Heart J. **9**:459, 1934.

6. Durant, T. M.; Ginsburg, I. W., and Roesler, H.: Transient Bundle Block and Other Electrocardiographic Changes in Pulmonary Embolism, Am. Heart J. **17**:423, 1939.

cardiographic pattern can exist in the absence of an organic change in the conduction system. As the matter now stands, knowledge regarding the exact pathogenesis of lesions capable of producing this electrocardiographic pattern is entirely inadequate. Histopathologic studies of human hearts in which the electrocardiogram conformed to the wide S wave pattern were reported by Mahaim [7] and by Evans and Turnbull.[8] Unfortunately, in these cases there was clinical evidence of gross coronary disease which may or may not have borne any etiologic relation to the lesion responsible for the particular feature (the wide S wave of the QRS complex) of the electrocardiogram. Until further studies of well selected cases become available it might be well to maintain an unbiased viewpoint regarding its exact pathogenesis. At least our studies have shown thus far that much more frequently than in other types of bundle branch block the lesion responsible for the wide S pattern may exhibit little if any evidence of progression—indeed, to a degree singularly foreign to the vast majority of cases of coronary sclerosis in a clinically recognizable form.

In so far as direct information regarding the causation of this lesion is lacking, we may examine the indirect evidence available in our material.

ETIOLOGIC FACTORS

Age Incidence.—The ages varied from 9 to 88 years. As previously noted,[1] the average age of 492 patients belonging to this group was 59.3 years at the time of the discovery of the lesion. The incidence by decades is shown in table 1, which indicates that the lesion was most frequently found in patients between the ages of 50 and 70.

Sex Incidence.—Males predominate over females to an extent even greater than in the other groups studied. The ratio for males to females with the wide S wave pattern was about 4 to 1.

Coronary Sclerosis and Hypertension.—A clinical diagnosis of coronary sclerosis without hypertension was made in 141 cases (29 per cent), of hypertensive heart disease without coronary sclerosis in 53 cases (11 per cent) and of hypertension and coronary sclerosis in 92 cases (19 per cent). That is, in almost 60 per cent of the cases a clinical diagnosis of coronary disease or hypertension, either independent or in association with one another, was made. In the analysis of the group, it is of interest to note that in 71 of the cases in which coronary disease was diagnosed the clinician made it clear that the diagnosis was based

7. Mahaim, I., cited by Wilson, F. N.; Johnston, F. D., and Barker, P. S.: Electrocardiograms of an Unusual Type in Right Bundle-Branch Block, Am. Heart J. **9**:472, 1934.

8. Evans, W.: The Newer Electrocardiogram Denoting Right Bundle-Branch Block, Lancet **2**:1127 and 1184, 1937 (pathological report by H. M. Turnbull).

on the electrocardiographic abnormality alone and that in an additional 144 cases in which cardiac symptoms could not be elicited no specific cardiac diagnosis was denoted for indexing purposes.

Rheumatic Heart Disease.—A diagnosis of rheumatic heart disease was made in 44 cases (9 per cent). In 25 of these the diagnosis made was mitral stenosis and insufficiency; in 3 additional cases mitral disease was associated with aortic disease, and in 13 cases the patients were found to harbor aortic disease. Other rheumatic cardiac manifestations were noted in 3 additional cases.

Syphilitic Aortitis with Aortic Insufficiency.—This diagnosis was made in 6 instances.

TABLE 1.—*Age Distribution of Patients with a Wide S Wave Pattern*

Age at Diagnosis, Years	Total		Males		Females	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
0- 9	2	0.4	2	0.5	..	....
10-19	2	0.4	2	0.5	..	....
20-29	7	1.4	4	1.0	3	3.1
30-39	19	3.9	16	4.1	3	3.1
40-49	56	11.4	46	11.6	10	10.3
50-59	139	28.3	101	25.6	38	39.2
60-69	182	37.0	150	38.0	32	33.0
70-79	76	15.4	65	16.5	11	11.3
80-89	9	1.8	9	2.3	..	....
Total	492	100	395	100	97	100
Average age	59.3 yr.		60.0 yr.		58.0 yr.	

Congenital Heart Disease.—In 6 cases the clinical findings warranted a diagnosis of congenital heart disease, and in some of these strong evidence of septal involvement existed. In the remaining cases various miscellaneous conditions existed which do not merit special mention.

A CONSIDERATION OF PATIENTS WHO WERE EXAMINED ON MORE THAN ONE OCCASION

An electrocardiogram was recorded on more than one occasion for 65 of the 492 patients considered in the group with the wide S wave pattern. In 36 of these 65 patients the electrocardiographic pattern remained unchanged over periods as long as sixteen years after the original electrocardiogram indicating the presence of the wide S wave pattern was recorded. In 12 patients additional changes which were absent on the original electrocardiogram, such as changes in the T wave, prolongations of the PR interval and ectopic rhythms, were noted at a

subsequent examination, but in all these the QRS complex itself remained essentially unaltered.

There were 14 patients whose cases were of special interest in so far as the wide S wave pattern developed during the period of observation. In a critical analysis of their records, it was noted that in 2 patients the wide S wave pattern developed after an acute attack of coronary thrombosis and that in 3 a wide S wave pattern developed after the patients had been known to be subjects of angina pectoris. When the anginal syndrome was first noted all three had normal electrocardiograms. One patient with essential hypertension who had had a normal electrocardiogram before an episode of congestive heart failure showed a wide S wave pattern after the episode. There was nothing, however, in the history of the remaining 8 patients to indicate why the electrocardiograms had changed from a normal pattern to one with wide S waves. Moderate hypertension existed in 3 of the 8 patients. At the completion of this study, 5 of the 8 patients were still alive (at 64, 65, 66, 67 and 71 years, respectively), and none of them presented any cardiac symptoms with the exception of 1 very obese patient who complained of dyspnea on moderate exertion. The 3 patients who had died reached the ages of 65, 73 and 78, respectively. The cause of death was stated to be cerebral hemorrhage in 2 instances and coronary thrombosis in the third, at the age of 73. The cases of the remaining 3 patients are also of special interest and require comment. Two of these represent the only examples of our series in which the disturbance indicated by the wide S wave pattern progressed into bundle branch block of the concordant variety. The third is the only instance in our series in which a patient with bundle branch block of the discordant type reverted later to a wide S wave pattern.

REPORT OF CASES

CASE 1.—A woman, then 47 years old, was first seen in 1925, at which time she had exophthalmic goiter, for which thyroidectomy was done. Her electrocardiogram then showed the auricles to be fibrillating; the T wave in lead I was inverted, but the ventricular complexes were normal. Her weight then was 267 pounds (121.1 Kg.). Her dyspnea was attributed to obesity and to hyperthyroidism. Two years later her electrocardiogram was essentially the same except that the T wave in lead I was now upright (fig. 3). In 1929 her electrocardiogram was a typical example of a wide S wave pattern. There was no evidence of cardiac decompensation, and she was found at this visit to have diabetes. In 1934 her electrocardiogram showed bundle branch block, with the T waves diphasic in lead I. The QRS complexes measured from 0.14 to 0.16 second. She was dyspneic as before, but there was no evidence of actual congestive heart failure

or of coronary insufficiency. When she was seen a year later, she had had two cerebral vascular accidents, and she died a few months later, presumably of cardiac disease.

CASE 2.—The patient was first seen in 1930, when he was 59 years old. This patient had had hyperthyroidism as well, for which thyroidectomy had been performed. The electrocardiogram showed a wide S wave pattern. No significant cardiac symptoms could be elicited, but in 1934 he returned with congestive heart failure. His blood pressure, which had been normal at the first visit, was now 210 mm. of mercury systolic and 104 mm. diastolic. The electrocardiogram showed a prolongation of the PR interval to 0.24 second, bundle branch block (the QRS interval measuring 0.12 second) and diphasic T waves in lead I. He died a few months later of recurrent congestive heart failure, at the age of 63.

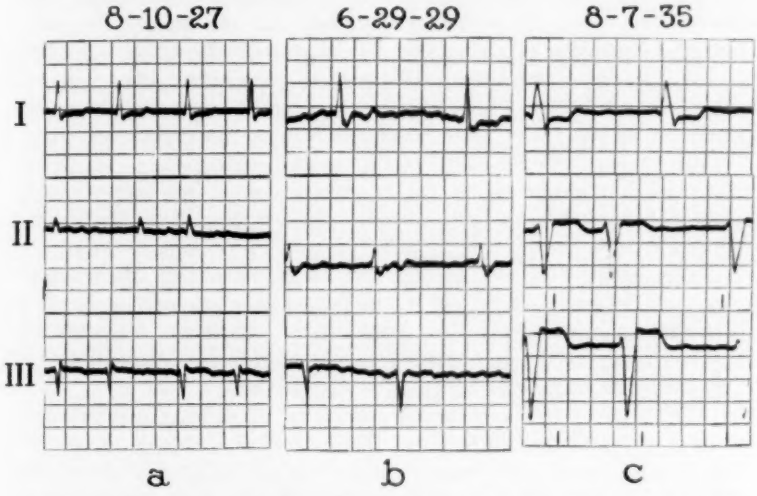

Fig. 3.—Three of the electrocardiograms belonging to case 1, showing that in 1927 the ventricular complexes were normal, that in 1929 a change had occurred in the ventricular complexes conforming to the wide S wave pattern and that in 1935 bundle branch block with concordant graphs existed. This patient died a year later, at the age of 58, presumably of heart disease. She had had at least two cerebrovascular accidents prior to death.

CASE 3.—A woman, then 56 years old, presented herself for examination in 1932, complaining principally of dizziness. She admitted that she was dyspneic on moderate exertion. An electrocardiogram then showed bundle branch block with discordant graphs (the QRS complex measuring 0.12 second), together with a 2:1 heart block. Determination of the basal metabolic rate gave —21 per cent, but the classic features of myxedema were absent. However, thyroid therapy was instituted, and three months later, when she was seen again, her basal metabolic rate was —3 per cent and she claimed that she was subjectively improved. The electrocardiogram then showed a wide S wave pattern with a prolongation of the PR interval to 0.24 second. At a recent examination this patient was found

to be in reasonably good health for her age; she is no more dyspneic on exertion now than she was in 1932, and she has taken thyroid off and on in amounts insufficient to control a true myxedematous condition. There is nothing about her present condition which suggests that she does have myxedema. The electrocardiogram is identical with the previous one, except that the PR interval now measures 0.28 second.

THE LIFE HISTORY OF PATIENTS WITH THE WIDE S WAVE PATTERN

The life expectancy curve and the death rate determinations for this group have been indicated in a previous article.[1] It was shown that patients with the wide S wave pattern follow a course considerably more favorable than those with bundle branch block with concordant and with discordant curves. It was also indicated that the highest mortality occurred during the first year after the diagnosis of the lesion was made and that this was even more pronounced in cases of the other types of bundle branch block. Those who survived the first few years after the discovery of the lesion were shown to have a life expectancy curve which roughly parallels that for the normal population. This being the case, it occurred to us that a comparison of the patients who succumbed in the earlier years following the discovery of the lesion with those who were living a considerable number of years later might supply the essential factors which contributed to the high mortality of the former patients. Otherwise stated, did certain factors exist among those persons who had a poor prognosis which were absent in those whose life history continued apparently uninfluenced by the disturbance responsible for this particular electrocardiographic configuration?

We therefore reviewed the records of the 92 patients (72 men and 20 women) who died during the first year after the discovery of the electrocardiographic abnormality, as well as the records of those who were still living ten years after the original diagnosis was made.

Patients Who Had Died by the End of the First Year.—This survey indicated that 26 of the 92 patients (28 per cent) died of noncardiac causes (malignant lesions, pneumonia, uremia associated with prostatic obstruction, Hodgkin's disease, postoperative peritonitis and so forth). It is to be recalled that the average age for the patient with the wide S wave pattern at the time the diagnosis was made was almost 60 years. Of the 26 patients whose death was attributable to noncardiac causes, 10 had severe hypertension (170 mm. of mercury systolic or more); in not a single patient was there congestive heart failure, but the condition of 2 was diagnosed as angina pectoris; 4 patients showed inversions of the T wave in leads II and III, and 2 showed inversions of the T wave in lead I; 5 patients had either roentgenologic or clinical evidence of cardiac hypertrophy. Of the remaining 66 patients of the number who died

within the first year after the lesion was discovered, 33 patients were known to have died as a direct result of cardiac disease. Of these 33 patients, 13 had a systolic blood pressure of 170 mm. of mercury or more or a diastolic blood pressure of 100 or more; 23 patients had either congestive heart failure or angina pectoris or both, and 25 had significant electrocardiographic findings (apart from the QRS abnormality and axis deviation), consisting in 6 instances of inversion of the T wave in leads I or II or both, in 10 instances of inversion of the T wave in leads II and III, in 2 instances of inversion of the T wave in leads I, II and III, in 1 instance of prolongation of the PR interval beyond 0.20 second and in 6 instances of auricular fibrillation. Twenty-four patients had evidence of cardiac hypertrophy, either clinical or roentgenographic or both.

There remain, then, 33 patients who died during the first year for whom the cause of death was not ascertainable, but the data relevant to these patients would tend to indicate that a fairly high proportion of them succumbed to cardiac disease. Thus, 14 patients had a systolic blood pressure of 170 mm. of mercury or more and/or a diastolic blood pressure of 100 mm. or more; angina pectoris and/or congestive heart failure was noted in 15; 7 had significant electrocardiographic findings (apart from the QRS abnormality and axis deviation), consisting of inversion of the T wave in lead I or II or both in 2 instances, inversion of leads II and III in 4 instances and auricular fibrillation in 1 instance; 24 were thought to show cardiac enlargement, either on clinical or on roentgenologic examination or on both.

Necropsy data were available for 16 patients of the number who died during the first year of observation. The details are given in table 2, which includes data on 4 additional patients who died after the first year of observation. It will be noted again that the patients who died as a result of heart disease (10 of the 20) had abundant evidence of cardiac involvement quite apart from the electrocardiographic abnormality under discussion. Frank evidence of myocardial or coronary insufficiency was recorded in all cases, and the weights of the hearts varied from 433 to 750 Gm. With 1 notable exception (case 17), in the remaining 10 cases in which death was attributable to noncardiac disease far lesser degrees of gross cardiac involvement were exhibited, both clinically and at necropsy. The average weight of the heart in these 9 cases (omitting case 17) was 409 Gm., as compared with 566 Gm. in the 10 cases in which death resulted from heart disease.

In summary, then, 26 of the 92 patients who died during the first year of observation succumbed to noncardiac disease, and among these there was relatively little evidence of cardiac crippling. In contrast, the

TABLE 2.—*Clinical and Necropsy Data for Patients with a Wide S Wave Pattern of the Electrocardiogram*

Case Number	Age, Years	Sex	Cardiac Symptoms *	Blood Pressure, Mm. of Mercury	Other Electrocardiographic Findings *	Causes of Death	Heart Weight, Gm.	Coronary Sclerosis, Grade	Comment
1	56	M	0	165/ 90	R. V. P.; inv. T in III	Peritonitis	340	1	
2	80	M	0	112/ 80	Di. T in II and III	Cancer	366	Not stated	
3	74	M	0	140/ 90	Di. T in II and III	Pneumonia	380	2+	Chronic rheumatic heart disease, aortic and mitral
4†	70	M	0	144/ 80	Inv. T in III	Pneumonia following operation on prostate gland	382	2	
5	85	F	0	200/ 90	R. V. P.	Pneumonia; pernicious anemia	404	1-2	
6	87	M	0	144/ 90	L. V. P.; inv. T in III	Pneumonia	432	2+	
7	67	M	0	156/ 82	L. V. P.; inv. T in III	Intestinal hemorrhage	445	Not stated	Chronic aortic endocarditis
8	72	M	0	120/ 80	None	Cancer	450	2	
9	77	M	0	180/ 90	L. V. P.; inv. T in III	Pyelonephritis	482	2	No myofibrosis
10	54	F	Cong. fail.	160/ 70	Inv. T in III	Cardiac	433	1	Mitral stenosis 2+
11	70	M	+	170/104	Inv. T in III	Cardiac	455	1	Hypertension
12	68	F	+	160/120	L. V. P.; di. T in II and III	Cardiac	490	2+	
13	67	M	+	142/ 90	PR = 0.22 sec.	Cardiac	540	1	
14	57	F	Cong. fail.	130/100	Aur. fib.	Cardiac	560	Not stated	
15	64	M	+	180/ 75	L. V. P.; di. T in II and III	Cardiac	560	2+	Syphilitic aortitis
16	75	M	Cong. fail.	142/ 90	L. V. P.; di. T in I	Cardiac	590	3+	Considerable myofibrosis
17†	62	M	Cong. fail.	170/ 90	Aur. fib.	Exophthalmic goiter; pernicious anemia; pneumonia	621	..	Infarct (healing) in left ventricle
18†	57	M	Cong. fail.; angina	200/120	Extreme L. V. P.	Cardiac	632	4	Considerable fibrosis
19	52	M	Angina	192/ 94	Inv. T in II and III	Cardiac	650	4	Syphilitic aortitis; old infarct in septum
20†	58	M	Cong. fail.	96/ 78	L. V. P.	Cardiac	750	3	Region of fibrosis in septum

* Cong. fail. indicates congestive failure; R. V. P., right ventricular preponderance; L. V. P., left ventricular preponderance; inv., inverted; di., diphasic, and aur. fib. auricular fibrillation.

† In this case death occurred after the first year of observation.

remaining 66 patients exhibited stigmas of organic heart disease in a high percentage of cases, both clinically and at necropsy, in addition to the electrocardiographic abnormality under consideration.

Patients Who Were Living Ten Years or More after the Original Diagnosis.—Returning now to the 62 patients who were still alive at the end of ten years after the discovery of the electrocardiographic abnormality, we find that at the time of the original examination the following data were recorded: Forty-seven were men and 15 were women. Nine patients had a systolic blood pressure of more than 170 mm. of mercury and/or a diastolic blood pressure of 100 mm. of mercury or more; 1 patient had had congestive heart failure; another patient gave a history of angina pectoris; 8 patients had electrocardiographic changes apart from the wide S wave pattern which required comment (6 with inversions of the T wave in leads II and III, 1 with inversion of the T wave in lead I and 1 with auricular fibrillation). Some evidence of cardiac enlargement was thought to exist in 19 patients, yet the lack of symptoms and of significant objective findings is well illustrated by the fact that in the cases of 33 of the 62 patients no specific cardiac diagnosis was made despite the electrocardiographic abnormality, and in an additional 9 instances the diagnosis of coronary disease was made on the electrocardiogram alone.

The Clinical Status of These Patients at the Last Inquiry.—Of the 62 patients with the wide S wave pattern who lived ten years or longer, 15 (24 per cent) had died and 47 (76 per cent) were living. Thirty-seven of the 47 regarded themselves as in good health; 8 were well while living on a restricted program, while 2 were not progressing favorably despite restrictions.

THE GENERAL INCIDENCE OF CARDIAC SYMPTOMS IN THE GROUP AS A WHOLE

It has been shown before [9] that, considering the group as a whole, angina pectoris and congestive heart failure, either independently or in association with each other, occurred in about 22 per cent of the patients at the time of the first examination which indicated the presence of the wide S wave pattern, and that for patients with bundle branch block with concordant graphs and bundle branch block with discordant graphs the corresponding figures were 44 and 37 per cent, respectively. Coronary occlusion was noted in 9 patients with the wide S wave pattern and in 17 and 37, respectively, of those with the discordant variety of bundle branch block and bundle branch block with concordant graphs.

9. Reeser, R., Jr.; Willius, F. A., and Dry, T. J.: Life Expectancy in Conductive Disturbances Affecting the Ventricular Complex of the Electrocardiogram: II. Special Consideration of Bundle Branch Block with Concordant Graphs and with Discordant Graphs, Arch. Int. Med., this issue, p. 1027.

COMMENT

Even though Oppenheimer and his co-workers [10] drew attention, in 1925, to the favorable course which patients with the wide S wave pattern often run, few writers have since made any effort to segregate cases of this type from those of other defects of bundle branch conduction. With a few exceptions, in fact, cardiologists in general have been loath to accept any deviation from the so-called normal electrocardiographic pattern as compatible with nonprogressive heart disease. That the carefully conducted follow-up study on 64 patients, by Wood, Jeffers and Wolferth [11] in 1935, has similarly failed to convince some writers that patients whose electrocardiograms exhibit the wide S wave type of conductive disturbance should be considered separately from the standpoint of prognosis is evident from the fact that in reports which have been published since that time these patients have been grouped along with those showing the conventional forms of conductive defects.

Evans and Turnbull [8] expressed the view that this type of electrocardiogram belongs to a separate group. In all the cases reported by them, however, there was obvious clinical evidence of organic heart disease, but it should be noted that the patients constituting the material for their study were from the cardiac disease department of the London Hospital and were, therefore, even less representative of a cross section of the general population than is the material in a general medical practice.

That the wide S wave pattern indicates a conductive disturbance occasioned by involvement of the right bundle branch is the view shared by most other investigators. Its exact pathogenesis, however, is but poorly understood. In the majority of cases the lesion was noted first in patients of middle life or older. The average age at the time of the discovery of the lesion differs but slightly from the average age at which are first encountered the other types (bundle branch block of either the concordant or the discordant variety) of conductive disturbance acknowledged to be due usually to coronary disease, either independently or in association with hypertension. Yet, by the same token, one encounters a strange paradox, for whereas coronary disease produces lesions which involve more predominantly the left bundle branch, all the available evidence points to the conclusion that the wide S wave pattern results from a lesion affecting the right bundle branch (predominantly, if not entirely, as in experimental lesions). In our group of cases of

10. Oppenheimer, B. S.; Rothschild, M. A., and Mann, H.: Cardiographic Differentiation of a Sub-Group of Intra-Ventricular Block with Observations on the Prognosis, J. Clin. Investigation **1**:592, 1925.

11. Wood, F. C.; Jeffers, W. A., and Wolferth, C. A.: Follow-Up Study of Sixty-Four Patients with a Right Bundle-Branch Conduction Defect, Am. Heart J. **10**:1056, 1935.

bundle branch block of the concordant variety (as defined by us) the ratio of cases of left bundle branch block to those of right bundle branch block was 733 to 23, a ratio in accordance with that noted by other writers. The sex incidence of the wide S wave type of conductive disturbance is the sex incidence of coronary disease. Indeed, men predominate to an even greater degree than they do in cases of the other types of conductive disturbances.

The frequency with which a clinical diagnosis of hypertension and coronary disease, either independently or in association with each other, was made has been indicated. The inference, again, is that the etiologic factors concerned in most cases of this group are coronary disease and/or hypertension. There are several points to be considered, however, before such a conclusion is unequivocally accepted: 1. We are concerned with patients who are already in the arteriosclerotic age and with the age when hypertension also is common, and one may well wonder whether the presence of coronary sclerosis is merely coincidental. 2. The frequency with which the diagnosis of coronary disease is made can be materially influenced by chance electrocardiographic evidence, for our records contain many instances in which the clinician indicated that the electrocardiographic information represented the only positive finding to substantiate such a diagnosis. This was true in relatively few patients with other types of conductive disturbance affecting the ventricular complex, because other evidence of organic heart disease occurred in most of the latter.

The analysis of cases belonging to this group in which rheumatic heart lesions were found is worthy of comment. Mitral disease predominated over aortic lesions in the proportion of about 2 to 1, which is exactly the reverse of what was found in cases of both concordant and discordant bundle branch block. Here, then, is a set of circumstances not in discordance with the general viewpoint that the wide S wave pattern is the electrocardiographic manifestation of a lesion involving the right bundle branch in so far as rheumatic heart disease, and especially mitral stenosis, are far more likely to result in predominantly right-sided bundle lesions than they are in predominantly left-sided lesions. When the wide S wave pattern was encountered in relatively young persons the lesion considered to be present was invariably congenital. In some there was definite evidence of septal involvement as indicated by the presence of cyanosis. It is to be remembered in this connection that the majority of congenital lesions involving the heart cause right ventricular strain, so that here again a rational etiologic relationship between the anatomic lesion and the electrocardiographic pattern becomes evident.

The degree of coronary sclerosis in those patients whose death was a result of noncardiac causes was minimal considering that with

1 exception the patients were in the seventh, eighth or ninth decade of life. Those whose hearts showed gross evidences of disease had, without exception, the clinical evidence necessary to permit the diagnosis of such disease, and the electrocardiographic evidence could safely have been dispensed with altogether in the appraisal of their cardiac status.

One other observation seemed important to us, namely, the infrequency with which the disturbance producing the wide S wave pattern was found to progress to bundle branch block of the concordant or the discordant variety. It would seem that if the etiologic factor concerned were common to all forms of conductive disturbance, the wide S wave pattern dependent on an admittedly less serious lesion would be seen as a transitional stage to the more serious forms of conductive defect more frequently than was our experience.

SUMMARY AND CONCLUSIONS

In the present state of knowledge the wide S wave pattern is to be regarded as indicating a disturbance affecting the right bundle branch. In so far as it is most commonly seen in middle age or after and in so far as it affects men much more frequently than it does women (facts which apply equally well to other forms of conductive disturbance), one may infer that the disturbance is produced by the same process as that which is responsible for other types of conductive defect, namely, coronary sclerosis, independently or in association with hypertension. In the analysis of a large series of cases, however, certain facts are revealed which need further elucidation before they can be reconciled with such a viewpoint. Thus, if it were accepted for the moment that the ischemic effects of coronary disease constitute the underlying factor in its production, we have no information available to explain why it should be predominantly a right-sided bundle lesion when clinical experience and histopathologic studies indicate that such pathologic processes as were just suggested produce predominantly left-sided lesions. This is exemplified by the ratio of 733 examples of left bundle branch block (as defined by us) to 23 examples of right bundle branch block (both of the concordant variety), an experience in accordance with the observations of others. Among those persons with rheumatic heart disease, the valvular lesion most commonly encountered is mitral stenosis, which could be expected to cause predominantly right-sided bundle lesions, but the patients with rheumatic heart disease constitute but a small minority of the entire group of patients exhibiting this type of electrocardiogram, and if it were essentially a manifestation of rheumatic heart disease, it should be more frequently encountered not only in younger persons than is actually the case but also more frequently in patients with other stigmas of previous rheumatic infection.

In short, if we are dealing with an arteriosclerotic process, its behavior is rather out of keeping with the life history of coronary sclerosis in general; indeed, some of the hearts which were examined at necropsy showed remarkably little evidence of coronary sclerosis, considering the age of the patients concerned. If we are dealing with a rheumatic process we have to assume a minimal lesion which in the vast majority of cases has not caused any valvular lesion at all and a limited myocardial lesion at the most, and this is not in keeping with the life history or the incidence of rheumatic heart disease. We await the results of histopathologic studies in suitable cases with the hope that such studies may reveal both the distribution of the lesion and its intrinsic causation.

On the basis of clinical follow-up information, however, we are prepared to champion its classification into a separate subgroup among the conductive defects involving the ventricular complex and to regard it as a relatively benign lesion with a good prognosis when unattended by coexistent findings indicative of organic heart disease. This is especially true if the electrocardiographic abnormality has been known to be present for a year or longer.

URINARY PROTEIN PARTITIONS IN AMYLOID NEPHROSIS

SAMUEL BERG, M.D.*
NEWARK, N. J.

Urinary secretion is a mechanical process during which water and solutes are filtered from the blood through the glomerular membranes, while the plasma proteins are retained. Proteins in the urine in abnormal amounts are plasma proteins which have passed through permeable glomeruli; only insignificant amounts originate in the tubules. The mechanical process of glomerular filtration is further evidenced by the fact that protein molecules below a molecular weight of approximately 70,000 (that of hemoglobin) readily escape through the glomeruli, whereas larger protein molecules are usually retained; in other words, the larger the molecular size of the urinary protein, the greater is the glomerular lesion. The albumins, being the smallest of plasma proteins, should appear earliest and in greatest amounts in the urine under abnormal renal conditions. The globulins, which are much larger, should appear only when more severe lesions are present and in lesser amounts than the albumins. Fibrinogen, the largest of all plasma proteins, should appear only in the most advanced disturbances and then only in small quantities. Determination of the protein partitions in the blood and in the urine have been made by many investigators in all types of nephropathies, with extremely conflicting results. A survey of the literature from 1882 to 1926 can be found in an article by Hiller, McIntosh and Van Slyke.[1]

METHOD

In an endeavor to study the physiology of protein excretion by diseased kidneys in greater detail, protein partitions were determined on individual twenty-four hour specimens of urine collected according to the schema of Mosenthal's two hour test for renal function. Simultaneous plasma protein values were obtained.

All the patients studied were men with clinically proved amyloidosis complicating tuberculosis. The daily diet contained 125 Gm. of proteins and a total of 2,700 calories. Salt was considerably restricted, small amounts being used only for

* Formerly assistant attending physician, Sea View Hospital.

From the Metabolic Service of Sea View Hospital, Staten Island, N. Y.; Dr. Herman O. Mosenthal, Director.

1. Hiller, A.; McIntosh, J. F., and Van Slyke, D. D.: The Excretion of Albumin and Globulin in Nephritis, J. Clin. Investigation **24**:235-252 (June) 1927.

flavoring during cooking and none at table. Fluids were limited to 1.5 liters per day. Blood proteins were determined either by the Howe method of protein partitioning with sodium sulfate and the micro-Kjeldahl technic, or by partitioning with ammonium sulfate and measuring the proteins quantitatively by Exton and Rose's scopometric technic.[2] Only the latter method was used to determine the urinary proteins.

DATA ON CASES

CASE 1.—C. S., aged 26, was admitted in June 1927. The diagnosis was Pott's disease with a draining sinus in the right groin and productive pulmonary lesions. The congo red test showed 100 per cent absorption several times in 1939 and 1940.

TABLE 1.—*Proteins (Mg.) Excreted in Urine (case 1)*

Time	Volume, Cc.	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio *
8-10 a.m.	60	564	316	0	880	1.78
10 a.m.-12 m.	120	588	272	0	860	2.16
12 m.-2 p.m.	195	545	245	0	790	2.22
2-4 p.m.	155	457	258	0	715	1.77
4-6 p.m.	95	480	275	0	755	1.74
Total, day	625	2,634	1,366	0	4,000	1.92
Total, night	1,020	1,580	670	0	2,250	2.36
Total	1,645	4,214	2,036	0	6,250	1.92

Examinations made April 12, 1940.

* When dividing the quantity of albumins by the quantity of globulins to determine the albumin-globulin (A/G) ratio, one should remember that fibrinogen is one of the globulins and should be included with them.

TABLE 2.—*Proteins (Mg.) Excreted in Urine (case 2)*

Time	Volume, Cc.	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8-10 a.m.	220	247	138	77	385	1.15
10 a.m.-12 m.	210	200	62	0	262	3.22
12 m.-2 p.m.	185	194	46	0	240	4.22
2-4 p.m.	145	340	131	26	471	2.06
4-6 p.m.	210	336	105	0	441	3.20
Total, day	970	1,317	482	113	1,799	2.21
Total, night	1,000	1,150	200	0	1,350	5.75
Total	1,970	2,467	682	113	3,149	3.10

Examinations made Sept. 30, 1939.

CASE 2.—A. G., aged 30, was admitted in October 1930 and discharged in May 1940. The diagnosis was tuberculous cavities in both lungs and tuberculous laryngitis and enteritis. The congo red test has shown 100 per cent absorption six times in the past four years.

CASE 3.—R. O., aged 30, was admitted in November 1930 and died in October 1939. Autopsy revealed healed tuberculous lesions in the lungs, tuberculous empyema on the right side, tuberculous mesenteric lymphadenitis, tuberculous tracheitis, miliary tuberculosis and considerable amyloidosis of the kidneys, liver, spleen and adrenal glands.

2. Exton, W. G., and Rose, A. R.: Clinical Partition of Blood Proteins by Scopometry, J. A. M. A. **99**:1236-1239 (Oct. 8) 1932.

Case 4.—M. N., aged 57, was admitted in April 1932 and died in December 1939. The diagnosis was tuberculous cavities in both lungs, tuberculous enteritis, tuberculous epididymitis with draining sinus and amyloidosis. The congo red test has shown 100 per cent absorption five times since 1935.

Table 3.—*Proteins (Mg.) Excreted in Urine (case 3)*

Time	Volume, Cc.	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8-10 a.m.	160	624	456	136	1,080	1.05
10 a.m.-12 m.	110	555	425	71	980	1.12
12 m.-2 p.m.	215	484	301	86	785	1.25
2-4 p.m.	200	500	350	100	850	1.11
4-6 p.m.	220	616	364	121	980	1.26
Total, day	905	2,779	1,896	514	4,675	1.14
Total, night	505	3,105	1,515	176	4,620	1.83
Total	1,410	5,884	3,411	690	9,295	1.43

Examinations made April 27, 1939.

Table 4.—*Proteins (Mg.) Excreted in Urine (case 4)*

Time	Volume, Cc.	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8-10 a.m.	90	378	328	76	706	0.93
10 a.m.-12 m.	110	380	340	0	720	1.12
12 m.-2 p.m.	60	300	162	39	462	1.49
2-4 p.m.	60	255	198	36	453	1.09
4-6 p.m.	105	365	354	0	719	1.03
Total, day	425	1,678	1,382	151	3,060	1.09
Total, night	450	1,035	810	0	1,845	1.27
Total	875	2,713	2,192	151	4,905	1.11

Examinations made Oct. 18, 1939.

Table 5.—*Proteins (Mg.) Excreted in Urine (case 5)*

Time	Volume, Cc.	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8-10 a.m.	85	395	221	0	616	1.77
10 a.m.-12 m.	80	384	196	0	580	1.90
12 m.-2 p.m.	70	333	185	0	518	1.85
2-4 p.m.	180	315	252	0	567	1.27
4-6 p.m.	65	308	166	0	474	1.85
Total, day	480	1,735	1,020	0	2,755	1.70
Total, night	1,000	1,500	750	0	2,250	2.00
Total	1,480	3,235	1,770	0	5,005	1.85

Examinations made Sept. 20, 1939.

Case 5.—E. R., aged 55, was admitted in January 1933 and died in April 1940. Autopsy revealed cavities in both lungs, Pott's disease of the dorsal portion of the spine, tuberculous enteritis, caseous mesenteric lymphadenitis and amyloidosis of the liver, spleen, kidneys, adrenal glands, stomach and intestine.

Case 6.—S. S., aged 49, was admitted in January 1934. The diagnosis was tuberculous cavities in both lungs, tuberculous empyema on the right side and tuberculous osteochondritis of the first rib, with a draining sinus. The congo red test showed 100 per cent absorption in 1939.

CASE 7.—A. D., aged 29, was admitted in August 1935. The diagnosis was tuberculous cavities in both lungs and tuberculous prostatitis, epididymitis and vesiculitis. The congo red test showed 100 per cent absorption in 1939 and 1940.

CASE 8.—E. C., aged 24, was admitted in December 1935. The diagnosis was tuberculous cavities in both lungs and tuberculous empyema on the left side. The

TABLE 6.—*Proteins (Mg.) Excreted in Urine (case 6)*

Time	Volume, Cc.	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8-10 a.m.	200	354	0	0	354	....
10 a.m.-12 m.	190	1,254	0	0	1,254	....
12 m.-2 p.m.	150	328	0	0	328	....
2-4 p.m.	90	243	0	0	243	....
4-6 p.m.	135	458	0	0	458	....
Total, day	765	2,637	0	0	2,637	....
Total, night	565	1,836	0	0	1,836	....
Total	1,330	4,473	0	0	4,473	....

Examinations made May 6, 1940.

TABLE 7.—*Proteins (Mg.) Excreted in Urine (case 7)*

Time	Volume, Cc.	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8-10 a.m.	180	319	212	0	531	2.36
10 a.m.-12 m.	75	495	427	46	922	1.04
12 m.-2 p.m.	230	504	140	0	644	3.60
2-4 p.m.	70	189	161	17	350	1.06
4-6 p.m.	130	440	307	32	747	1.30
Total, day	685	1,947	1,247	95	3,194	1.55
Total, night	590	1,922	1,043	20	2,965	1.82
Total	1,275	3,869	2,290	115	6,159	1.69

Examinations made May 6, 1940.

TABLE 8.—*Proteins (Mg.) Excreted in Urine (case 8)*

Time	Volume, Cc.	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8-10 a.m.	70	90	0	0	90	....
10 a.m.-12 m.	100	138	0	0	138	....
12 m.-2 p.m.	105	123	0	0	123	....
2-4 p.m.	55	80	0	0	80	....
4-6 p.m.	60	90	0	0	90	....
Total, day	390	521	0	0	521	....
Total, night	900	607	0	0	607	....
Total	1,290	1,128	0	0	1,128	....

Examinations made April 23, 1940.

congo red test showed 70 per cent absorption in 1937 and 100 per cent absorption in 1938.

CASE 9.—P. D., aged 37, was admitted in June 1936. The diagnosis was tuberculous cavities in both lungs and hydrothorax on the left side. The congo red test showed 90 per cent absorption in 1936, 100 per cent absorption in January

and June 1937, 90 per cent absorption in November 1937 and 65 per cent absorption in 1938 and 1939.

CASE 10.—J. C., aged 24, was admitted in September 1936 and died in October 1939, from severe hemoptysis. The diagnosis was tuberculous cavities in both lungs, hydrothorax on the right side, tuberculous enteritis and amyloidosis.

TABLE 9.—*Proteins (Mg.) Excreted in Urine (case 9)*

Time	Volume, Cc.	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8-10 a.m.	190	184	0	0	184	....
10 a.m.-12 m.	230	150	0	0	150	....
12 m.-2 p.m.	230	99	0	0	99	....
2-4 p.m.	230	265	0	0	265	....
4-6 p.m.	150	145	0	0	145	....
Total, day	1,030	843	0	0	843	....
Total, night	1,300	2,925	0	0	2,925	....
Total	2,330	3,768	0	0	3,768	....

Examinations made April 12, 1940.

TABLE 10.—*Proteins (Mg.) Excreted in Urine (case 10)*

Time	Volume, Cc.	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8-10 a.m.	100	392	288	56	680	1.13
10 a.m.-12 m.	300	645	435	0	1,080	1.60
12 m.-2 p.m.	285	608	399	0	1,007	1.78
2-4 p.m.	105	267	163	0	430	1.74
4-6 p.m.	120	246	162	0	408	1.47
Total, day	970	2,248	1,447	56	3,695	1.49
Total, night	1,270	1,905	825	0	2,730	2.22
Total	2,240	4,153	2,272	56	6,425	1.78

Examinations made April 21, 1939.

TABLE 11.—*Proteins (Mg.) Excreted in Urine (case 11)*

Time	Volume, Cc.	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8-10 a.m.	100	210	198	0	408	1.03
10 a.m.-12 m.	80	196	180	0	376	1.08
12 m.-2 p.m.	120	294	270	0	564	1.08
2-4 p.m.	110	335	265	0	600	1.27
4-6 p.m.	105	247	236	0	483	1.03
Total, day	515	1,282	1,149	0	2,431	1.11
Total, night	800	2,160	1,640	0	2,800	1.30
Total	1,315	3,442	2,789	0	5,231	1.27

Examinations made April 30, 1940.

CASE 11.—W. L., aged 31, was admitted in January 1938. The diagnosis was tuberculous cavities in both lungs, hydrothorax on the left side, ulcerative tuberculosis of the right kidney and syphilis. The congo red test showed 100 per cent absorption.

CASE 12.—N. P., aged 31, was admitted in April 1938. The diagnosis was tuberculous cavities in both lungs and tuberculous laryngitis. The congo red test showed 100 per cent absorption.

TABLE 12.—*Proteins (Mg.) Excreted in Urine (case 12)*

Time	Volume, Cc.	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8-10 a.m.	185	721	269	0	990	2.68
10 a.m.-12 m.	165	602	231	0	833	2.68
12 m.-2 p.m.	135	550	253	0	803	2.22
2-4 p.m.	110	841	72	0	913	11.69
4-6 p.m.	135	1,114	168	0	1,282	6.63
Total, day	730	3,828	993	0	4,821	3.85
Total, night	500	2,600	400	0	3,000	6.50
Total	1,230	6,428	1,393	0	7,821	4.61

Examinations made April 30, 1940.

TABLE 13.—*Proteins (Mg.) Excreted in Urine (case 13)*

Time	Volume, Cc.	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8-10 a.m.	155	511	209	0	720	2.44
10 a.m.-12 m.	110	456	149	0	605	2.92
12 m.-2 p.m.	125	343	107	0	450	3.20
2-4 p.m.	80	256	52	0	308	5.00
4-6 p.m.	115	350	133	0	483	2.68
Total, day	585	1,916	650	0	2,566	2.94
Total, night	680	1,700	442	0	2,142	3.84
Total	1,265	3,616	1,092	0	4,708	3.30

Examinations made April 27, 1939.

TABLE 14.—*Proteins (Mg.) Excreted in Urine (case 14)*

Time	Volume, Cc.	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8-10 a.m.	280	1,470	1,162	378	2,632	0.95
10 a.m.-12 m.	200	1,280	370	240	1,650	2.10
12 m.-2 p.m.	160	1,000	632	128	1,632	1.31
2-4 p.m.	230	1,300	425	174	1,725	2.01
4-6 p.m.	240	1,092	924	300	2,016	0.89
Total, day	1,110	6,142	3,513	1,220	9,655	1.29
Total, night	1,240	3,286	2,232	0	5,518	1.43
Total	2,350	9,428	5,745	1,220	15,173	1.35

Examinations made April 21, 1939.

CASE 13.—C. H., aged 53, was admitted in May 1938 and died in August 1939. Autopsy revealed tuberculous cavities in both lungs, tuberculous enteritis and laryngitis, caseous mesenteric lymphadenitis and amyloidosis of the kidneys.

CASE 14.—S. R., aged 35, was admitted in November 1938 and died in May 1939. Autopsy revealed tuberculous cavities in both lungs; tuberculous laryngitis

and enteritis; caseous mesenteric lymphadenitis; considerable amyloidosis of the spleen, pancreas, adrenal glands and kidneys but not of the liver, and terminal endocarditis and uremia.

Case 15.—H. S., aged 38, was admitted in March 1939. The diagnosis was tuberculous cavities in both lungs and generalized tuberculous lymphadenopathy. The congo red test showed 85 per cent absorption in November 1939.

Case 16.—H. F., aged 41, was admitted in August 1939. The diagnosis was tuberculous cavities in both lungs, tuberculous enteritis and fistula in ano, tuberculous cervical adenitis with a draining sinus and ulcerative tuberculosis of the kidneys. The congo red test showed 100 per cent absorption twice in 1939.

Table 15.—*Proteins (Mg.) Excreted in Urine (case 15)*

Time	Volume, Cc.	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8-10 a.m.	140	679	203	0	882	3.30
10 a.m.-12 m.	Not collected					
12 m.-2 p.m.	95	427	301	0	728	1.43
2-4 p.m.	85	304	104	0	408	2.92
4-6 p.m.	135	533	122	0	655	1.37
Total, day	455	1,943	730	0	2,673	2.66
Total, night	900	2,395	755	0	3,150	3.17
Total	1,355	4,338	1,485	0	5,823	2.92

Examinations made April 30, 1940.

Table 16.—*Proteins (Mg.) Excreted in Urine (case 16)*

Time	Volume, Cc.	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8-10 a.m.	65	840	135	0	975	6.22
10 a.m.-12 m.	55	616	44	0	660	14.00
12 m.-2 p.m.	75	780	120	0	900	6.50
2-4 p.m.	25	302	38	0	340	7.94
4-6 p.m.	45	423	45	0	468	9.40
Total, day	265	2,961	382	0	3,343	7.75
Total, night	500	3,650	600	0	4,250	6.08
Total	765	6,611	982	0	7,593	6.73

Examinations made April 23, 1939.

COMMENT

Blood Proteins in Amyloid Nephrosis.—Most investigators have found extremely diminished values for blood proteins in cases of amyloid nephrosis accompanied by severe proteinuria. Owing to the more rapid elimination of albumins than of globulins through the kidneys, the former show a much greater relative decrease than the latter, with a corresponding distinct drop in the albumin-globulin ratio. The variations in this series are all in the same direction but to a much less noticeable degree than in any other published study. It is evident that values for blood proteins can be maintained at physiologic levels, without formation of

edema, by diets supplying sufficient nitrogen in cases in which the excretion of protein in the urine is as high as 15 Gm. a day. These values are shown in table 17.

Urinary Albumin-Globulin Ratios in Amyloid Nephrosis.—Again, most observers have stated that the urinary albumin-globulin ratio in cases of amyloid nephrosis accompanied by profuse proteinuria is lower than that associated with any other type of nephropathy, being usually under 2 and certainly under 5. In 12 of our cases the ratios were in accord with this observation, and in another (case 16) the ratio was only slightly higher. Globulins were not found in the urine in 3 cases (6, 8

TABLE 17.—*Values for Blood Proteins*

	Blood					Urine	
Case No.	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio	Total Protein	A/G Ratio
1.....	3.5	2.8	0.4	6.7	1.25	6.25	2.16
2.....	3.4	2.7	0.4	6.5	1.26	3.15	3.10
3.....	3.2	2.7	0.4	6.3	1.18	9.20	1.43
4.....	3.1	2.6	0.5	6.2	1.19	4.50	1.11
5.....	2.9	2.7	0.5	6.1	1.07	5.00	1.85
6.....	4.5	2.3	0.5	7.3	2.00	4.47	†
7.....	3.9	2.4	0.5	6.8	1.62	6.15	1.60
8.....	4.1	2.3	0.4	6.8	1.80	1.12	†
9.....	3.5	2.7	*	6.2	1.30	3.76	†
10.....	3.1	2.8	0.5	6.4	1.11	6.42	1.78
11.....	4.4	2.3	0.6	7.3	1.91	5.23	1.27
12.....	3.9	2.5	*	6.4	1.56	7.82	4.61
13.....	3.2	2.8	0.4	6.4	1.14	4.70	3.30
14.....	3.2	2.8	0.4	6.4	1.14	15.17	1.35
15.....	3.8	2.5	0.3	6.6	1.52	5.82	2.92
16.....	3.7	2.5	0.5	6.7	1.50	7.50	6.73

* No determinations made.
† No globulin in urine.

and 9) despite noticeable proteinuria in 2 of them, so that globulinuria is not necessarily associated with amyloid nephrosis.

Table 17 shows that there is no definite relationship between the albumin-globulin ratio of the blood and the albumin-globulin ratio of the urine when plasma proteins are maintained near low normal levels by adequate genesis. Several authors expressed the belief that the albumin-globulin ratio of the blood influences the proportions of albumins and globulins excreted by the kidneys; as Bing stated in 1936,[3] when the relative percentage of albumin in the urine is especially low in patients with amyloidosis it is due to corresponding conditions in the blood. Contradicting this view are the data in case 11, in which the plasma proteins showed normal total and relative values, yet the urinary albumin-globulin ratio was very low.

3. Bing, J.: Studies in Proteinuria, Copenhagen, Levin & Munksgaard, 1936.

Urinary Changes and Progress of Amyloid Nephrosis.—Table 18 presents the data for 4 patients for whom there was an appreciable difference in time between examinations of the urine. All had rapidly progressive disease. Two of the patients (cases 4 and 5) died shortly after the last examination. This table indicates that the excretion of globulins increases at a much faster rate than that of albumins and that the urinary albumin-globulin ratio is, therefore, a better index of progress than determination of the total urinary proteins.

TABLE 18.—*Instances of Changes in the Amount of Proteins (Mg.) Excreted in the Urine*

	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
Case 1					
Oct. 4, 1939	4,108	1,745	0	5,853	2.34
Six months later	4,214	2,036	0	6,250	2.07
Case 4					
April 27, 1939	1,689	853	0	2,542	1.97
Six months later	2,713	2,192	151	4,905	1.15
Case 5					
May 4, 1939	1,782	559	0	2,341	3.19
Four months later	3,235	1,770	0	5,005	1.82
Case 7					
April 23, 1939	4,688	1,167	0	5,855	4.01
Thirteen months later	3,869	2,290	115	6,159	1.61

TABLE 19.—*Hourly Excretion of Urinary Proteins (Mg.)* *

Case No.	Day	Night	Case No.	Day	Night
1	400	160	9	65	209
2	180	96	10	369	195
3	467	330	11	243	271
4	306	132	12	482	214
5	275	169	13	256	153
6	264	131	14	965	394
7	361	212	15	267	225
8	52	43	16	334	303

* Day specimens were collected from 8 a.m. to 6 p.m. and night specimens from 6 p.m. to 8 a.m.

Excretion of Protein in Day and in Night Urine.—It is well known that the excretion of protein in the urine per unit of time is increased after the ingestion of food and during activity; in this series the hourly output of urinary proteins during the day was greater than that during the night in 14 of the 16 cases (table 19). No reason could be found for this reversal in cases 9 and 11.

Urinary Albumin-Globulin Ratios for the Day and for the Night.—Accompanying this nightly decrease in protein excretion was an increase in the urinary albumin-globulin ratio (table 20), which was due to a greater relative drop in the globulin output than in the albumin output.

Apparently, this regular decrease is due to nonfunction of the more severely affected glomeruli during the night hours, when the demands on the kidneys are less.

Bearing on this phase of renal function are the observations in relation to the escape of fibrinogen. This protein, which has an extremely large molecule, escaped in the urine in 6 cases (tables 2, 3, 4, 7, 10 and 14), and only in cases 3 and 7 was it present in both day and night specimens. In all the other instances it was not present in the night samples; case 14 was especially noteworthy in this respect, for fibrinogen was excreted in all the day specimens in amounts varying from 64 to 189 mg. per hour, yet none was found in the night urine. This observation seems to support the explanation for the decrease in protein excretion, with increase in the urinary albumin-globulin ratio, in the night specimens; that is, the more severely affected glomeruli function only when the need for renal function is great and cease to function as the load diminishes.

TABLE 20.—*Urinary A/G Ratios during Day and Night*

Case No.	Day	Night	Case No.	Day	Night
1	1.92	2.36	9	....	....
2	2.21	5.75	10	1.49	2.22
3	1.14	1.83	11	1.11	1.30
4	1.09	1.27	12	3.85	6.50
5	1.70	2.00	13	2.94	3.84
6	....	....	14	1.29	1.43
7	1.44	1.80	15	2.66	3.17
8	....	....	16	7.75	6.08

SUMMARY AND CONCLUSIONS

Physiologic levels of plasma proteins have been maintained by the administration of high protein diets in cases of amyloid nephrosis in which up to 15 Gm. of protein was excreted a day.

The synthesis of fibrinogen is not impaired by the presence of heavy deposits of amyloid in the liver.

The albumin-globulin ratio of the blood does not influence the albumin-globulin ratio of the urine.

The urinary proteins in cases of advanced renal amyloidosis usually, but not always, contain high percentages of globulins; in fact, globulins may be absent entirely.

The albumin-globulin ratios of day urines were uniformly lower than the albumin-globulin ratios of night urines.

Fibrinogen is found fairly often in the urine in cases of amyloid nephrosis in which the patient excretes large proportions of globulins, and in this series it was always found during the day, with customary activity, and never during the night, with rest.

Changes in the urinary albumin-globulin ratios are a better index of progress of the renal lesions in amyloid nephrosis than estimation of the total protein excretion in the urine.

The hourly excretion of proteins and the urinary albumin-globulin ratios during the day are variable in patients on high protein diets under the usual daily routine in a sanatorium.

In itself, determination of the urinary protein fractions is of no value in the differential diagnosis of amyloid nephrosis.

From an analysis of the content of albumin, globulin and fibrinogen of the urine, it appears that all the glomeruli do not take an active part in urinary secretion throughout the day, rather that the more severely affected glomeruli function only when an increased demand is made on the kidneys and that the less severely affected glomeruli function during basal conditions.

156 Roseville Avenue.

Progress in Internal Medicine

DISEASES OF THE HEART

A REVIEW OF SIGNIFICANT CONTRIBUTIONS MADE DURING 1940

ASHTON GRAYBIEL, M.D.
WITH THE EDITORIAL ASSISTANCE OF PAUL D. WHITE, M.D.
BOSTON

The second World War is having an increasingly important effect in the field of medicine. Modern total warfare, which is directed against nations as a whole and is fought with psychologic, as well as the usual, implements of war, has created medical problems which, in magnitude and scope, are without parallel. A further consequence of this conflict is the interruption or subversion of many scientific endeavors. A number of the universities in Europe have been forced to suspend all their activities and others have become geared to the war machine. This change in emphasis has not been without its effect on problems relating to the cardiovascular system. Accordingly, a section of the review is devoted to brief consideration of some of these problems.

HEART DISEASE AND THE WAR.

Examination of the Heart.—Inasmuch as clinical examination of the heart has attracted the attention of most physicians for many years it might seem that little could remain for further discussion in regard to the selection of military personnel. Nevertheless, a number of authors [1] have been moved to write on this subject, emphasizing those features of the cardiac examination deemed to be of chief importance in the examination of recruits and soldiers. The following summary is drawn from the sources just mentioned, from the recommendations of the subcommittee on cardiovascular disease of the National Research Council and from notes of our own.

The History: In civilian practice the most important feature of the cardiac examination is a detailed and careful history. This may offer the only clues of cardiac disorder or disability and afford the only means of tracing its development. In presenting his story and describing his symptoms the patient, with rare exceptions, cooperates wholeheartedly

From the Cardiac Clinic of the Massachusetts General Hospital.

1. (*a*) Parkinson, J.: Cardiac Examination in Wartime, Brit. M. J. **1**:428, 1940. (*b*) Bourne, G.: Examination of the Heart in Recruits, ibid. **2**:442, 1940.

with the physician. The same degree of cooperation may not always be secured by physicians in the military services. The person examined may wish to hide certain symptoms in order to obtain admission to, or promotion in, the armed forces. Conversely, symptoms may be exaggerated or falsely said to be present if it is desired to stay out of, or be relieved from, military duty. The able examiner should, however, be able to form the questions in such a manner as to force the malingerer or falsifier to answer inconsistently.

Despite the hazard just mentioned, the history must not be neglected. The examinee should be questioned regarding the occurrence of scarlet fever, diphtheria or rheumatic fever in youth and the presence of syphilis or a nervous disorder in later years, and inquiry should be made concerning the chief cardiac symptoms of pain, dyspnea, palpitation and undue fatigability. The symptomatic aspects of neurocirculatory asthenia will be discussed in detail under that heading. If there is doubt regarding the ease with which symptoms appear during or after exercise, an exercise tolerance test may be desirable. Finally, it must be kept in mind that with a decrease in reliability of the history there is a corresponding increase in the importance of the physical examination.

Inspection: General appearance may afford useful and important information. Anxiety may be declared by flushed skin, excessive sweating and dilated pupils. In rare instances slight cyanosis may be the only clinical sign of congenital heart disease. Conspicuous pallor or clubbing of the fingers may be the result of heart disease with associated infection. Vigorous pulsation of the arteries in the neck suggests essential hypertension, hyperthyroidism, aortic regurgitation, coarctation of the aorta or anxiety. Rapid respirations are often observed in persons with neurocirculatory asthenia. Other and more obvious signs of heart disease do not require repetition.

Clinical Estimation of Heart Size: Determination of the size of the heart is the single most important procedure of the examination, and the key to this determination is the location of the apex impulse. The lowest and outermost point of the impulse corresponds most nearly with the left lower border of the heart. If the heart is of normal size the left border will usually be found in the fifth intercostal space, inside the midclavicular line. If for some reason the heart is displaced upward so that the apex impulse is felt in the fourth intercostal space the normal position may be as much as 1 cm. outside the midclavicular line. If the apex impulse is felt in the sixth intercostal space it should be at least 1 cm. within the midclavicular line or cardiac enlargement may be suspected. The vigorous thrust of the overactive heart may be transmitted beyond the true apex beat, which may lead to error. Great care must be taken in these instances, and percussion may be helpful. If the heart is enlarged,

the left border, determined by percussion, either will coincide with the outer margin of the apex impulse or will be lateral to it. If the heart is not enlarged, the left border, determined by percussion, either will coincide with the outer margin of the apex impulse or will be medial to it. It should be remembered that scoliosis of the spine, fibrosis of the lungs, etc., may displace the heart and the apex beat.

Rate and Rhythm: If the heart rate is persistently over 100 beats a minute an explanation should be found. Such a rate does not necessarily indicate myocardial disease, as many physicians believe, but does indicate a functional disturbance which may be explained by anxiety, neurocirculatory asthenia, poor training, fever, thyrotoxicosis, etc. The underlying cause, rather than the heart rate per se, should be the determining factor in evaluating tachycardia.

If the heart rate is slower than 50 beats a minute the person should be exercised in order to show that a satisfactory rise in rate occurs. If the heart rate is 40 or less there is a possibility that heart block is present even though a moderate increase in rate occurs with exercise; an electrocardiogram should be taken.

If waxing and waning of the heart rate with respiration proves confusing, the rhythm should be determined while the subject holds his breath. Extrasystoles are usually of little or no significance and can be abolished with exercise. The absolute irregularity of auricular fibrillation is ordinarily readily appreciated, and the irregularity increases with exercise. Rapid (over 120 beats a minute) regular rhythms which do not change in rate with exercise require electrocardiographic study.

Sounds and Murmurs: In the timing of all heart sounds and murmurs it is recommended [2] that the examiner fix in mind the position of the sharp second sound in the cardiac cycle as heard at the base of the heart. The examiner may then move the stethoscope toward the apex, keeping in mind the proper relation of the first and second heart sounds. Accentuation of the first sound at the mitral area may be physiologic but should draw sharp attention to the possible presence of a mitral diastolic murmur. Diminution in intensity of this sound is an unreliable sign of heart disease, unless the diminution is extreme and cannot be explained by other factors, such as a thick chest wall or emphysema. Accentuation of the second sound at the aortic area is usually associated with increased circulatory rate, with increased blood pressure in the aorta or with disease of the aorta. Accentuation of the second sound at the pulmonary area is often present in healthy young persons under the excitement of examination but may indicate pulmonary hypertension (most commonly dependent on mitral stenosis or failure of the left ventricle).

2. Examination of the Heart, prepared by the Committee on Leaflets and Pamphlets of the American Heart Association, New York.

Splitting or reduplication of the first sound at the mitral area is the result of asynchronism in the early phases of contraction of the two ventricles. It is usually not a sign of heart disease, but if it is associated with splitting of the second sound as well it may be the result of block in one of the bundle branches and an electrocardiographic test may be warranted. Splitting or reduplication of the second sound at the base of the heart is the result of asynchronous closure of the pulmonary and the aortic valves. It rarely indicates heart disease but occasionally may be due to bundle branch block or to abnormally high aortic or pulmonary blood pressure.

Third heart sounds are commonly heard in healthy children or young adults and are of no pathologic significance.

The problem of the significance of heart murmurs resolves itself largely into a consideration of murmurs systolic in time, because continuous murmurs [3] and, with rare exceptions, diastolic murmurs should always be regarded as being pathologically significant. In the appraisal of a murmur occurring during systole the first step is to determine the point of maximal intensity and the second to trace its transmission to other valve areas or other locations over the chest. Systolic murmurs heard maximally at the aortic area are usually significant and indicate disease of the aortic valves, disease of the aorta itself or dilation of the aorta. Systolic murmurs heard maximally at the pulmonary area are rarely of pathologic significance. They are variable in character and intensity, often becoming louder if the subject shifts from the upright to the recumbent position or disappearing if the subject inspires deeply, or exercises. Systolic murmurs heard maximally at the mitral area are often, but not always, significant; they are the most difficult to evaluate. This difficulty is readily exemplified by the gradual disappearance of murmurs which occur in nearly 10 per cent of patients after an attack of rheumatic fever. In such instances there is, undoubtedly, a long period during which the murmur appears to be innocent. Generally speaking, loud or harsh systolic murmurs heard at the mitral area which are constant in character and are not abolished with change in position of the subject, deep respiration or exercise signify deformity of the mitral valve or other disease mechanism. Such murmurs are usually widely transmitted and can be heard at the axilla or over the bases of the lungs. Loud systolic murmurs heard maximally in the third intercostal space to the left of the sternum, frequently accompanied by a thrill, suggest a congenital interventricular septal defect. Precordial systolic murmurs

3. It is important not to interpret as due to a diseased condition the continuous venous hum, heard in the neck in many healthy young persons, which is sometimes transmitted down as far as the base of the heart. This hum can be easily obliterated by light pressure over the jugular veins.

not heard maximally at the area of a valve are usually cardiorespiratory in nature and are due to movement of air in the lungs resulting from the motion of the heart. Such murmurs readily change in character or are abolished as a result of change in the position of the subject, deep inspiration or exercise.

Blood Pressure: The physiologic variations in blood pressure occur so readily and are of such magnitude that normal blood pressure is difficult to define and is often a matter of individual opinion. Age, temperament, fitness and degree of anxiety are only a few of the many factors which may influence the level of blood pressure in a person at rest. In young persons there is far greater instability of both pulse rate and blood pressure than in older persons. Thus, a blood pressure of 170 mm. of mercury systolic and 80 mm. diastolic in a young, anxious recruit at the time of examination is of far less significance than a pressure of 140 mm. of mercury systolic and 95 mm. diastolic in a man of middle age. Such considerations have led many to the opinion that determinations of blood pressure should not be made routinely in the examination of recruits.

Parkinson [1a] believes the blood pressure should be determined if the apex beat is displaced or is forceful without other cause or if the aortic second sound is accentuated. He considers that only pressures of 160 mm. of mercury systolic and 90 mm. diastolic or higher which persist after the subject has had a "fair interval" of rest should be regarded with any misgiving. Bourne,[1b] also, calls attention to the "nervous increase" in blood pressure, presumably due chiefly to increased output, wherein the systolic pressure is temporarily raised to 170 or above but the diastolic pressure is little changed.

However, it may be desirable from a long range point of view to determine the blood pressure in every recruit, using whatever precautions are necessary to insure accuracy. Only by so doing can the comparatively large number of persons with hypertension be eliminated and the government be spared later expense of sickness benefits. The upper limit of blood pressure allowable for those under 25 years of age should be 150 mm. of mercury systolic and 80 mm. diastolic and for those over 25 years of age 140 mm. of mercury systolic and 90 mm. diastolic. Even this limit would include a number of persons in whom essential hypertension will probably develop. If higher readings are found it is certainly worth the time and effort to obtain subsequent readings after the subject has rested or to repeat the test another day. If persistently high readings are obtained in an emotionally stable person it is almost certain that arterial hypertension is present. If high readings are obtained in an emotionally unstable person his fitness for duty is open to grave doubt; many of those in whom neurocirculatory asthenia later develops will certainly be recruited from the ranks of those with persistently high blood pressure.

Electrocardiographic Tests: An electrocardiographic test is rarely indicated in the routine examination of recruits for the regular service of the army or navy. In the examination of older personnel the use of the electrocardiogram in selected cases will prove of great value. In those branches of the service which demand the ultimate in physical fitness, such as aviation, electrocardiographic tests should have wide application. It must be realized, however, that the range of normal electrocardiographic findings is greater than has been appreciated and that great judgment and experience must be exercised in the interpretation of doubtful records.

Roentgenologic Studies: Much the same might be said in regard to roentgen ray examination as was said previously in regard to electrocardiographic tests. In cases in which there is doubt, especially in regard to the size or shape of the heart, the use of the roentgen ray is invaluable.

Exercise Tolerance Tests: There is great and widespread disagreement among competent cardiologists regarding the value of arbitrary tests designed to measure the functional capacity of the heart. The tendency is to consider such tests as measuring general physical fitness or vasomotor stability, rather than heart reserve. In most instances it is sufficient simply to inquire into the ability of the subject to perform work or exercise which will afford a rough approximation of the ease with which cardiac symptoms appear. After such inquiry, if the examiner is still in doubt, it may prove worth while actually to observe the subject's response to some exercise test. If the diagnosis of neurocirculatory asthenia is suspected an easy test is sufficient; otherwise a more strenuous test is indicated. The easier the test the more exact the criteria which may be applied; in judging response to strenuous tests such individual factors as age, weight, degree of fitness and state of training must be taken into consideration.

In England, a committee assisted by the Cardiac Society of Great Britain and Ireland, by Sir Thomas Lewis and by Dr. Paul Wood [4] has recommended the use of the following exercise tolerance test:

1. The pulse rate is taken for fifteen seconds with the man standing.

2. The man places one foot on a chair at least fifteen inches in height, the other foot on the floor. He then raises himself until both feet are on the chair and the body is upright, then lowers himself until one foot is on the floor. This is repeated twenty times in sixty seconds. The man may use the back of the chair to steady himself when getting on and off the chair.

3. The pulse rate is then taken for fifteen seconds.

4. The man stands still, and forty-five seconds later—that is, one minute after the completion of the exercise—the pulse is taken for fifteen seconds (by which time the rate should be the same as, or lower than, the original rate), and the persistence of any dyspnea or distress noted.

4. Effort Syndrome, Brit. M. J. **2**:201, 1940.

The data thus ascertained are (i) the rise of pulse rate produced by the exercise, (ii) the degree of return to the constant standing pulse rate, (iii) the persistence of any dyspnea and (iv) any other signs of distress. If the man's original pulse rate is regained in sixty seconds and there is no residual dyspnea or distress, he may be regarded as possessing good exercise tolerance. If the response is unsatisfactory, the cause may lie in nervous instability or in some cardiovascular defect, and must be investigated by the appropriate examinations, to which the test must be considered as an adjunct. The test does not in itself afford conclusive evidence of these conditions or of a man's unfitness for Grade I; moreover, experience has shown that the response to this test may be rendered misleading in an otherwise healthy man by temporary toxemia—for example, the common cold—or by temporary lack of fitness following prolonged sedentary work or other causes.

Neurocirculatory Asthenia.—The chief contribution to the knowledge of heart disease resulting from the American Civil War was Da Costa's recognition of the "irritable heart" of soldiers, and the chief contribution during the first World War was reemphasis of this syndrome by Sir Thomas Lewis. This disorder, which is usually termed neurocirculatory asthenia, or effort syndrome, although important in peacetime, becomes outstandingly important in wartime. Hence the present great revival of interest in the syndrome and the great desire to avoid the mistakes of the past. Because neurocirculatory asthenia is a disorder in which psychologic features predominate and somatic features are merely the expression thereof, psychiatrists have attempted to include this syndrome as part of their special domain. This challenge has been met by the cardiologists, but they are, at this time, on the defensive, having failed over a long period to make any appreciable headway in regard either to diagnosis or to treatment. The idea of collaboration between cardiologists and psychiatrists apparently has not sufficiently recommended itself.

Importance: The importance of neurocirculatory asthenia in wartime is strikingly shown by Lewis'[5] figures. He points out that during the first World War there was 1 case of sickness referable to the cardiovascular system for every 4 cases of wound. By the summer of 1918 no fewer than 70,000 soldiers in the British Army who reported sick were classed as having cardiovascular conditions, but not more than 1 in 6 suffered from disease of the heart; the rest exhibited the effort syndrome. Later on, 44,000 of them became pensioners. Lewis does not share the view held by some that the problem of effort syndrome in this war will be different from what it was in 1914. Although no figures are yet available, there is every indication that Lewis' point of view will be justified.

Etiologic Factors: The fundamental cause of neurocirculatory asthenia is to be sought in the psychologic characteristics of the person, which are the result of hereditary and of environmental influences. The

5. Lewis, T.: The Soldier's Heart and the Effort Syndrome, ed. 2, London, Shaw & Sons, Ltd., 1940.

precipitating factors may be psychologic or physical or, as is often the case, a combination of the two. The sharp rise in incidence during wartime is simply due to the greater stresses and strains attending warfare. Some persons break down under trivial stresses, and for them the margin between breaking down and being able to carry on is narrow and precarious. In this group symptoms often develop while persons are in training and long before they are ready for combat duty. But the majority breaking down, as Lewis [5] points out, do not break on training but on duty which may involve hard physical labor, exposure to heat and cold, excessive fatigue, loss of sleep and, above all, fear, noise and the shock of battle. The British retreat from Dunkirk provides an excellent illustration.[6] Here, a large number of men were subjected to a mass experiment in which almost all had to undergo somewhat comparable degrees of danger and strain. All must have suffered, but in the majority no serious symptoms developed and recovery from the ordeal was rapid. In a few who were more susceptible there developed neurotic or anxiety symptoms of various kinds which have necessitated long-continued treatment.

Symptoms: Breathlessness is a cardinal symptom. In fact, some believe that neurocirculatory asthenia is an anxiety state complicated by hyperventilation. However, this view is not generally held, and Sargant [7] has recently emphasized that overventilation with its train of symptoms may properly be considered only as part of the whole syndrome. Lewis [5] believes that the breathlessness of effort syndrome is to be distinguished from hysterical and cardiac breathlessness (and well it may be in typical examples). Hysterical breathlessness is present even at rest, while in neurocirculatory asthenia it is in response to effort or excitement. Cardiac breathlessness is also provoked by exercise but is usually deep, not shallow, and is rarely rapid.

Pain or discomfort in the chest is a frequent complaint. It is usually brought on by exercise or excitement, is commonly dull or aching and may last for hours. In some instances the pain is sharp or stabbing and may occur in various parts of the chest or in other parts of the body. In rare instances the pain radiates to the left arm, and under such circumstance it may be difficult to differentiate from the pain of angina pectoris.

Palpitation is a frequent symptom and consists chiefly in consciousness of rapid, forceful heart action. It is usually related to excitement or to exertion and is not present at rest.

Easy fatigability is often a pressing complaint, and, as Lewis points out, when it can be gaged, is an excellent index of the severity of the disease.

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6. Neurotics in the Forces, Lancet **2**:299, 1940.
7. Sargant, W.: The Hyperventilation Syndrome, Lancet **1**:314, 1940.

Other symptoms include faintness and easy fainting, giddiness, tremor, sweating and nervousness.

Therapy and Prognosis: In the military services prophylaxis should be the keynote. The great importance of this is forcibly brought out by the fact that of men with neurocirculatory asthenia in the British forces sent to hospital during the first two years of the last war 43 per cent had symptoms on enlistment.[5] Thus, the tremendous disease problem occasioned by this disorder could have been nearly halved simply by keeping such men out of the services. For those in whom the malady develops while on duty, prompt and adequate treatment will restore some to health, and the remainder should be discharged. The usual treatment consists of a careful search for all foci of infection, repeated reassurance that heart disease is not present and a restful, hygienic regimen, with carefully graded exercise. It is probable that psychotherapy should play a more important role than it does at present. While the prognosis for life is good, the prospect of a return to duty is only fair. Approximately one fourth of persons with this disease become fit again or are greatly improved; two thirds show no significant change, while the remainder become worse.

Conclusion: The problem of neurocirculatory asthenia, or effort syndrome, in wartime has been clearly defined by Lewis.[5] The first part of the problem is to keep men with this disorder out of the services. The second part is to prevent its development during the training period by a system of gradual induction into the new and rigorous conditions of army life. The third part concerns the treatment and sorting for future duty or discharge of those in whom this syndrome develops.

Injury of the Heart (Including Chemical Injury).—Chest wounds accounted for a large percentage of all injuries during the first World War,[8] and concomitant injury to the heart and the great vessels was frequently observed. In Ryle's[8b] series of 130 cases of penetrating wounds of the chest, the heart or the pericardium was directly involved in 7 per cent. Since the last war there have been two major advances in this regard which should prove of great value in the present conflict. The first is the improvement in operative technic and teamwork in treating injuries both of the heart and of the chest. The second is the increase in knowledge in respect to the recognition and understanding of traumatic heart disease. Prompt surgical aid may well save an appreciable number of victims of heart wound. Of particular importance is the recognition of and relief from cardiac tamponade (usually due to

8. (*a*) Gordon-Watson, C.: Penetrating Wounds of the Chest: More Experiences in the Last War, Lancet **2**:194, 1940. (*b*) Ryle, J. A.: Penetrating Wounds of the Chest: Experience in the Last War, ibid. **2**:62, 1940. (*c*) Anderson, R. G.: Non-Penetrating Injuries of the Heart, Brit. M. J. **2**:307, 1940.

hemopericardium). Until recently it was thought that nonpenetrating chest injuries rarely affected the heart, whereas it is now known that the heart may be severely damaged even when there are no visible signs of injury over the thorax. Anderson [8c] states that during the first World War only 1 case of nonpenetrating injury to the heart was reported. It is safe to say that in the present war much more attention will be given to injuries of this type.

Leinoff [9] has enumerated certain facts which help in the understanding of the mechanism involved in nonpenetrating injuries of the heart:

1. The heart is not a firmly imbedded organ, but on the contrary is free and attached at its base by the large vessels. This anatomical fact allows the heart to be thrown violently against the bony structures of the chest or else torn at its attachment and thus damaged.

2. A hollow viscus which is distended and under pressure is more liable to be damaged by an injury than a similar organ which is relaxed. During systole the heart wall is under tension and trauma at that moment may rupture or damage this organ.

3. In young chests the heart actually may be compressed between the sternum and spine.

4. Immediately preceding an injury the patient automatically fixes the chest in inspiration by closing the glottis and thus produces an excellent medium for the transmission of trauma from the chest wall to the internal viscera.

5. Sudden increases in the intravascular pressures may force the blood back into the heart with sufficient force to damage the endocardium and other layers of the heart. In the postmortem material which was studied subendocardial hemorrhages were found only in the left heart suggesting that a sudden back pressure was capable of producing this lesion.

6. The amount and type of heart damage depends on the quality and quantity of the trauma.

7. Trauma may be the activating factor in initiating potential disease.

8. One or a combination of these factors may act to produce heart damage.

He further points out that the diagnosis depends on (*a*) awareness of this clinical possibility; (*b*) history of a direct nonpenetrating injury to the chest; (*c*) a previous normal cardiovascular history, and (*d*) signs, symptoms or laboratory findings indicating damage to the heart and appearing in the great majority of the cases immediately after the injury and persisting thereafter.

Asphyxiant or lung-irritant gases,[10] of which phosgene is the most toxic and most important, have their most pronounced effects on the

9. Leinoff, H. D.: Direct Nonpenetrating Injuries of the Heart, Ann. Int. Med. **14**:653, 1940.

10. (*a*) Medical Treatment of Gas Casualties, Air Raid Precautions Handbook no. 3, London, His Majesty's Stationery Office, 1940. (*b*) Goldman, L., and Cullen, G. E.: Some Medical Aspects of Chemical Warfare Agents, J. A. M. A. **114**:2200 (June 1) 1940.

alveoli of the lungs. The essential lesions are pulmonary edema, rupture of the alveoli with hemorrhage and thrombosis of the pulmonary vessels. Pulmonary edema may result within two hours of gassing, at which time cyanosis and increased venous pressure are prominent signs and dilatation of the heart occurs. So far as we are aware the cardiac embarrassment resulting from this type of injury has not been carefully studied. It would appear that although the heart as a whole is affected, the chief strain is on the right ventricle, resulting in dilatation and failure. The condition might properly be classed as an example of acute or subacute cor pulmonale. Treatment includes venesection and administration of oxygen.

Aviation and the Cardiovascular System.—The evolution of man has occurred in those regions of the world with favorable climates, near or not far above the level of the sea. And the countless adaptations to this environment have resulted in a harmoniously organized and integrated human being of almost infinite complexity. Among the various body organs none affords a more beautiful illustration of this adaptation than does the cardiovascular system. Its fundamental purpose is accomplished with such ease that in normal persons at rest not more than a tenth of the functional capacity of the circulatory system is required. However, as man has sought and found methods of extending his power through mechanical means the limits of adaptation of the cardiovascular system were first reached and then exceeded. Man now considers it necessary, and in the exigiencies of war imperative, to subject himself to environmental conditions to which he was never adapted. In the air there is the desire to ascend at such great speeds, to fly at such great heights and to turn and dive with such great force that the critical level of the human organism for such activities is often exceeded. The major problems insofar as the cardiovascular system is concerned may be grouped under three main headings, namely, (1) anoxia, (2) centrifugal acceleration and (3) sudden lowering of barometric pressure.

Anoxia: When a person is subjected to decreasing partial pressures of oxygen in the air breathed there occurs a whole train of events which lead to collapse and death. These changes begin with a decrease in the amount of oxyhemoglobin, which is associated with (or followed by) an increase in pulmonary ventilation. This increase in pulmonary ventilation is largely the result of stimulation via the carotid body and leads to a lowering of the carbon dioxide tension first in the alveoli and then in the arterial blood. The proportion of free carbon dioxide removed is greater than the proportion of combined carbon dioxide, and since the alkalinity of the blood is measured by the ratio of free to combined carbon dioxide, the net effect is to increase the alkalinity of the blood. The final result is a significant modification of many functions and properties of the blood and, of course, of the rest of the body as well.

The direct effect of anoxemia on the heart is difficult to measure. If this organ is healthy it will continue to function even after the subject has collapsed or has become unconscious. With increasing anoxemia there occurs compensatory dilatation of the coronary vessels, so that utilization of oxygen by the heart muscle, if conclusions drawn from animal experiments are valid, remains unchanged, even with extreme degrees of anoxia. Maurer [11] has found that in dogs there is increased lymph production during exposure to low oxygen tension. That the damage to cardiac blood capillaries was significant was shown not only by the greatly increased flow of cardiac lymph, but by the persistence of this increased flow even after long exposure to pure oxygen and by the appearance of erythrocytes in the lymph.

In normal subjects the brain suffers first, and objective signs of deterioration appear at elevations of 8,000 to 10,000 feet (2,438 to 3,048 meters). Patients with heart disease present another problem, and there is much evidence in some cases that signs or symptoms of cardiac embarrassment may result from exposure to low oxygen tensions.

The recent suggestion [12] that the normal heart is significantly affected by sudden ascents to elevations as low as 5,000 feet (1,524 meters) cannot be accepted. The only evidence given in support of this supposition is minor electrocardiographic alterations. To argue that such changes indicate myocardial impairment is wholly unwarranted and gains no support from practical experience.

Rapid ascents to altitudes of about 30,000 feet (9,144 meters) may result in unconsciousness without fainting,[13] but if the ascent is more gradual about half of the subjects faint and the other half lose consciousness without fainting. Fainting, or circulatory collapse, may be heralded by changes in pulse rate and in blood pressure, but often these changes are not great until the moment of collapse. In many normal persons an increase in heart rate is observed at oxygen tensions corresponding to elevations of 4,000 feet (1,219 meters), and if the oxygen tension is gradually lowered until the point of collapse is reached, the final heart rate may be only 16 or 18 beats higher than the control level but sometimes is much higher. Under the same circumstances different patterns of blood pressure response may be noted. In some instances there is little change until collapse occurs, but more commonly there is a gradual rise in systolic and a fall in diastolic pressure. Sometimes there is a fall

11. Maurer, F. W.: The Effects of Decreased Blood Oxygen and Increased Blood Carbon Dioxide on the Flow and Composition of Cervical and Cardiac Lymph, Am. J. Physiol. **131**:331, 1940.

12. White, M. S.: The Effect of Anoxia in High Altitude Flights on the Electrocardiogram, J. Aviation Med. **11**:166, 1940.

13. Armstrong, H. G.: Principles and Practice of Aviation Medicine, Baltimore, Williams & Wilkins Company, 1939.

in both systolic and diastolic pressures, which continues until the subject suddenly faints. Generally speaking, the adverse effects of asphyxia on the cardiovascular system are prevented by the administration of oxygen at elevations of 10,000 feet (3,048 meters) or higher. However, even if 100 per cent oxygen is breathed, the partial pressure of oxygen rapidly falls below normal at elevations above 33,000 feet (10,058 meters).[14]

Another adverse influence on the cardiovascular system is that of centrifugal forces which may be encountered during the combat maneuvers of modern fighter aircraft.[15] The effects of positive accelerations in the longitudinal axis of the body are observed most dramatically in the displacement of blood from the upper to the lower portions of the body. Forces greater than four to five times gravity acting for three seconds cannot be sustained without the occurrence of symptoms. If the force acts only for a short time, the blood supply to the eyes and then to the brain becomes deficient and there occurs a "veiling" of vision, or the "blackout." If the centrifugal force acts sufficiently long, return of venous blood to the heart becomes inadequate and complete circulatory collapse ensues. It is readily apparent that there are a number of practical problems in this connection which await solution. And these problems will become increasingly difficult in direct proportion to the increasing maneuverability of fighter aircraft.

Still another hazard which must be considered is that of aeroembolism.[13] When the atmospheric pressure is suddenly decreased, as occurs during rapid ascents to high altitudes, symptoms arise as a result of the formation of gas bubbles in the body tissues and fluids. This bubble formation takes place in accordance with laws governing the solubility of gases. Blood passing through the lungs is exposed to the gases in the atmosphere, and each gas is absorbed according to its partial pressure. Relatively large amounts of nitrogen go into solution because of its high partial pressure, while oxygen and carbon dioxide are taken off in smaller amounts. The body has special transport systems for oxygen and for carbon dioxide but none for nitrogen, which is relatively inert and obeys the laws of simple solution. Now, if the atmospheric pressure is decreased the body tissues and fluids tend to give up the dissolved gases, principally nitrogen, by way of the lungs. If the decrease is sudden and of the order of half an atmosphere or more, so that the concentration of nitrogen is at least double what it should be, this gas comes out of solution and forms bubbles, to which are added some oxygen, carbon dioxide and water vapor from the surrounding blood and tis-

14. Boothby, W. M.; Lovelace, W. R., II, and Benson, O. O.: High Altitude and Its Effect on the Human Body, J. Aero. Sc. **7**:461, 1940. Armstrong.[13]

15. von Diringshofen, H.: Medical Guide for Flying Personnel, translated by V. E. Henderson, London, Oxford University Press, 1940. Armstrong.[13]

sues. Nitrogen is much more soluble in fats and oils than in water, and body fats at blood temperature dissolve five to six times as much nitrogen per unit mass as does the blood itself. Because the elimination of nitrogen from the body is entirely through the blood stream those parts of the body with the poorest blood supply are the least able to lose their excess nitrogen rapidly. Blood loses its excess nitrogen first and fatty tissue last. There is considerable difference in opinion regarding the height of ascent before clinical symptoms appear. Armstrong states that gas bubbles are found in the spinal fluid at 18,000 feet (5,486 meters), while bubbles in the blood and tissues generally have not been found below 30,000 feet (9,144 meters). He believes symptoms are rarely noted below 30,000 to 35,000 feet (9,144 to 10,668 meters). However, other observers are forming the opinion that symptoms may appear at lower altitudes than these. The most dangerous symptoms occur, of course, when bubbles appear in the blood stream. Aeroembolism of a cerebral artery may lead to severe disturbance of the central nervous system, while if the coronary arteries are involved heart failure may result. This, then, becomes an important problem, especially in military aviation.

Submarine Medicine.—Many of the medical problems related to diving and to the use of submarines bear a close resemblance to those of aviation.[16] Most of the problems are concerned with respiration and the interchange of gases under pressure in the tissues of the body. Although modern submarines are air conditioned and the percentages of oxygen and of carbon dioxide and the degree of humidity are carefully controlled, there are many occasions, such as occur during practice in the use of the rescue lung in diving and in rescue work, when the environmental conditions are abnormal. Anoxia, excessive carbon dioxide and caisson disease, or bends, are some of the fields in which there is a demand for additional information. The care required in the selection of personnel for submarine duty is second only to that required in the selection of pilots.

PHYSIOLOGIC CONSIDERATIONS

Recent studies on the lymphatic vessels of the heart and on cardiac lymph of the dog are of considerable interest. Patek [17] has described in detail the three plexuses of lymphatics in the dog's heart. The lymphatic capillaries in the subendocardium drain into the extensive myocardial plexus, which in turn drains into the large and small lymphatic capillaries under the epicardium. From here the lymph passes into collecting trunks

16. Johnson, L. W.: Medical Problems of Diving and Submarines, New York State J. Med. **40**:1065, 1940.

17. Patek, P. R.: The Morphology of the Lymphatics of the Mammalian Heart, Am. J. Anat. **64**:203, 1939.

which accompany the coronary vessels and eventually unite into a single vessel which drains the entire heart.

Drinker and his associates [18] inserted a cannula into this lymphatic vessel beyond the point of its emergence from the pericardium, near the anterior surface of the pulmonary artery. Reasons are given for believing that the lymph collected by means of this cannula represents the complete lymph flow from the heart and from no other structures. It was found that this flow is uniform while circulatory conditions remain constant but that the flow varies directly with the vigor of the heart beat. The pressure in the cardiac lymphatic was measured in 2 instances and was found to be 14.1 and 15.5 cm. of lymph, respectively. The protein in the lymph varied from 2.50 to 4.73 mg. per hundred cubic centimeters, and averaged 3.69 mg., in 18 experiments on different dogs. Cardiac lymph is a filtrate from the blood capillaries. Like lymph from all other parts of the body, it contains serum albumin and serum globulin and it clots. Drinker and associates found that if horse serum or acacia is given intravenously it is soon detectable in the cardiac lymph.

These authors point out that under normal circumstances the function of the lymphatics in the heart is obviously the same as in other parts of the body, namely, to remove the protein-containing tissue fluid from the part and, after passage through a lymph node, to return it to the circulation. The question is raised regarding the significance of the lymphatic drainage in various types of heart disease.

Maurer, Warren and Drinker [19] studied the composition of mammalian pericardial fluid and reached the conclusion that it is merely slightly diluted lymph. It is in fact a filtrate from the epicardial blood capillaries, which passes not only through their endothelial walls, but through the epicardial endothelium. The average protein content of the pericardial fluid from 34 dogs was 1.7 mg. per hundred cubic centimeters, and the presence of fibrin was shown by rapid clotting immediately after removal from the animal.

SIGNS AND SYMPTOMS

Bloomfield,[20] in reviewing the question of dysphagia in disorders of the heart and the aorta, found that this sympton may be associated with five cardiovascular lesions, namely, (1) dilatation of the left auricle

18. Drinker, C. K.; Warren, M. F.; Maurer, F. W., and McCarrell, J. D.: The Flow, Pressure, and Composition of Cardiac Lymph, Am. J. Physiol. **130**: 43, 1940.

19. Maurer, F. W.; Warren, M. F., and Drinker, C. K.: The Composition of Mammalian Pericardial and Peritoneal Fluids: Studies of Their Protein and Chloride Contents, and the Passage of Foreign Substances from the Blood Stream into These Fluids, Am. J. Physiol. **129**:635, 1940.

20. Bloomfield, A. L.: Dysphagia with Disorders of the Heart and Great Vessels, Am. J. M. Sc. **200**:289, 1940.

(usually with mitral stenosis), (2) pericarditis, (3) saccular aneurysm, (4) dissecting aneurysm and (5) anomalies of the aortic arch or of the great vessels springing from it. He points out:

> The term "dysphagia" has been applied . . . not only to *difficulty* in swallowing but also to *pain on swallowing* without any feeling of obstruction. Dysphagia may be due to compression or to spasm. . . . In either case . . . symptoms may be transient or persistent.

Marked compression of the esophagus frequently exists, however, without any interference with swallowing. This is particularly well illustrated in patients with enlargement of the left auricle, only a few of whom complain of difficulty in swallowing. Dysphagia with pericarditis is a rare event, and Bloomfield was forced to turn to older treatises for detailed accounts. It would appear that actual difficulty in swallowing probably occurs only when the esophagus is compressed by a large effusion; hence this symptom may be of practical diagnostic importance. Dysphagia is a symptom frequently associated with saccular aneurysm, particularly of the descending aorta, but even here it has often been noted that marked compression of the esophagus exists without any complaint on swallowing. Mild dysphagia is usually due to reflex esophageal spasm and is of no serious import, but severe and persistent dysphagia is often of grave prognostic importance, since it may indicate either a false aneurysm or a threatened rupture into the esophagus. In cases of dissecting aneurysm dysphagia may be a more frequent symptom than reports would indicate because it is overshadowed by other more distressing symptoms; in the differential diagnosis of coronary occlusion and dissecting aneurysm the presence of dysphagia favors the latter.

METHOD

Johnston and Kline [21] have presented the results of tests, carried out with an acoustic model, which were designed to measure the efficiency of different types of stethoscopes in regard to both the end pieces and the tubing. They point out:

> The stethoscope in use is but one part of an acoustic system made up of (1) a source producing vibrations within the body which are transmitted through tissues, relatively dense as compared with air, to the wall of the chest, (2) the stethoscope, which receives vibrations at the surface of the skin and transmits them to the ear, and (3) the ear itself, which permits one to hear the vibrations as sounds.

They found that the response of any unit is much more dependent on the choice of the end piece than on the nature of the tubes, a conclusion which was supported by theoretic considerations. The most satis-

21. Johnston, F. D., and Kline, E. M.: An Acoustical Study of the Stethoscope, Arch. Int. Med. **65**:328 (Feb.) 1940.

factory bell was found to be one with as large an aperture as is practical and with a shallow air chamber; the addition of a rubber nipple over the terminal portion of a bell improved the latter's performance. In regard to the Bowles end piece, it was found that the diaphragm acts as a filter to suppress the transmission of low-pitched sounds but that the diaphragm must be stiff to be effective in this respect. The addition of a soft rubber sheath over the Bowles end piece materially improved its performance.

In conclusion Johnston and Kline point out that while some stethoscopes are better acoustic instruments than others in that they transmit more sound energy to the ear, loudness is of no importance except in regard to sounds that are so faint as to be nearly inaudible. They stress the importance, nevertheless, of having an intimate acquaintance with the kind of sound one is listening for and of being able to differentiate and interpret properly what is heard.

Segall [22] has described a method for the determination of systolic and diastolic blood pressure by palpation. This is accomplished by inflating the blood pressure cuff and holding the thumb over the site of the brachial artery—firmly enough to feel vibrations which are ordinarily detected with the stethoscope, but lightly enough to escape feeling arterial pulsation. These vibrations are first felt as short sharp sensations (systolic pressure) as air is released from the cuff; they become weaker as the cuff is deflated but gradually become stronger than ever (diastolic level), after which no sensation can be felt. Segall [23] has now made over 2,000 observations comparing the palpation and the auscultation method. He has learned to expect the systolic pressure to be 10 mm. of mercury higher by palpation and the diastolic pressure 10 mm. of mercury lower by auscultation, whenever there are any differences. He points out that the method of palpation is of particular value to physicians with impaired hearing and in the determination of low blood pressures, such as obtain in shock.

CARDIAC ARRHYTHMIAS

Wiggers [24] has made an important contribution to the understanding of ventricular fibrillation, which, in some respects, is the most significant of all the cardiac arrhythmias. He points out that in man it is a frequent cause of death following coronary occlusion or electrocution (accidental or purposeful) and is the apparent cause of sudden death following the inhalation of chloroform, benzene, cyclopropane and other vapors. It may even prove to be a frequent cause of sudden death following injury to the chest, with or without obvious injury to the heart.

22. Segall, H. N.: A Note on the Measurement of Diastolic and Systolic Blood Pressure by the Palpation of Arterial Vibrations (Sounds) over the Brachial Artery, Canad. M. A. J. **42**:311, 1940.

23. Segall, H. N.: Personal communication to the reviewers.

24. Wiggers, C. J.: The Mechanism and Nature of Ventricular Fibrillation, Am. Heart J. **20**:399, 1940.

Wiggers defines ventricular fibrillation as "an incoordinate type of contraction which, despite a high metabolic rate of the myocardium, produces no useful beats." He believes that recovery is rare in man even when the ventricles are "entirely normal." In records of over 400 cases of ventricular fibrillation in dogs there was only a single recovery.

In a summary of the facts from various studies so far completed it is apparent that ventricular fibrillation is initiated by a highly localized stimulus. This stimulus must reach a certain strength, however, or only a premature beat results. Late systole constitutes the period when the ventricle is especially vulnerable to stimuli, and this has been termed the vulnerable phase of systole. The capacity to fibrillate is inherent in heart muscle and does not require the sensitizing action of nerves or the presence of epinephrine or related substances, although these factors may affect the fibrillating threshold.

Ventricular fibrillation is conceived as an evolution of changes from the moment of its inception until it ceases completely, which is within thirty to forty-five minutes. Wiggers describes in some detail four stages of this evolution. The first, or undulatory, stage lasts for only a second or two and consists of three to six undulatory contractions which have many of the earmarks of premature systoles. The second stage, that of convulsive incoordination, lasts from fifteen to forty seconds and is characterized by more frequent waves of contraction which sweep over smaller sections of the ventricles, but inasmuch as not all masses contract in phase, the ventricles are pulled about in a convulsive manner. The third stage, that of tremulous incoordination, lasts two to three minutes, and in this the surface of the ventricles appears to be broken up progressively into smaller and smaller independently contracting areas. The fourth stage, that of atonic fibrillation, develops when the increasing anoxia caused by cessation of coronary flow results in the depression of contractile force. It is characterized by the slow passage of feeble contraction wavelets a short distance over the ventricular surface.

Wiggers [25] has clearly defined some of the requirements which must be fulfilled for successful cardiac resuscitation from ventricular fibrillation in dogs as follows:

1. Fibrillation must cease completely in every fraction of the myocardium. If even a vestige of fibrillating muscle remains, coordinate contractions never develop.

2. Adequate pacemakers must survive in order to initiate impulses with an excitatory value which is sufficient to inaugurate coordinated contraction.

25. Wiggers, C. J.: The Physiologic Basis for Cardiac Resuscitation from Ventricular Fibrillation: Method for Serial Defibrillation, Am. Heart J. **20**:413, 1940.

3. Not too many pacemakers—preferably one—should dominate the re-excitation of the defibrillated ventricle, for if too many act, they cause reversion to fibrillation.

4. The muscle fractions which are so excited must be capable of responding with reasonably vigorous contractions; otherwise, weak, coordinated beats result, and the heart dies in a hypodynamic state or reverts to fibrillation.

In regard to the first requirement, it is shown that fibrillation can be more readily abolished if, instead of a single strong countershock, three to seven weaker shocks are applied at intervals of one or two seconds. This procedure has been termed serial defibrillation. As regards the second and third difficulties, Wiggers has shown that the viability of pacemakers and of contracting myocardium can be assured by efficient cardiac massage, which restores coronary flow and relieves anoxia. The use of stimulating drugs, such as epinephrine and calcium salts, cannot be expected to benefit an anoxic mammalian heart and, after reoxygenation, usually sets up multiple pacemakers which tend to cause reversion to fibrillation.

He discusses the difficulties of meeting the aforementioned conditions in attempting to revive human fibrillating hearts and concludes:

Although the problem of reviving human fibrillating hearts must not be considered hopeless, we must not yet allow ourselves and others to expect too much in a practical way from our present methods until the next fundamental forward step is taken, viz., provision of oxygen for the fibrillating ventricle by methods other than massage. Since we lack suggestions in this direction, it would seem more profitable for the present to direct research talents toward the problem of reducing the sensitivity of the ventricle to the agents which cause fibrillation, with the hope, eventually, of making the heart completely refractory to fibrillation.

CONGENITAL HEART DISEASE

Ligation of the patent ductus arteriosus (uncomplicated by infection) has now been performed in more than 25 cases,[26] with an operative mortality of about 7 per cent. The results have been gratifying, and not only have there been improvement in the physical condition and increase in exercise tolerance, but the likelihood of the dreaded complication bacterial endocarditis has been lessened or abolished.

Eppinger and Burwell [27] studied the dynamics of the circulation in patients with patent ductus arteriosus before and after closure of the ductus. They point out that when there is a shunt of blood from the

26. Gross, R. E.: Experiences with Surgical Treatment in Ten Cases of Patent Ductus Arteriosus, J. A. M. A. **115**:1257 (Oct. 12) 1940; Surgical Closure of the Patent Ductus Arteriosus, J. Pediat. **17**:716, 1940. Jones, J. C.; Dolley, F. S., and Bullock, L. T.: The Diagnosis and Surgical Therapy of Patent Ductus Arteriosus, J. Thoracic Surg. **9**:413, 1940.

27. Eppinger, E. C., and Burwell, C. S.: The Mechanical Effects of Patent Ductus Arteriosus on the Heart and Their Relation to the X-Ray Signs, J. A. M. A. **115**:1262 (Oct. 12) 1940.

aorta through the ductus into the pulmonary artery it simply goes through the lungs and is returned to the left side of the heart, from which it left. This shunt not only serves no useful purpose but acts to decrease the peripheral flow and place a strain on the left side of the heart. The magnitude of the shunt was such that, under the conditions of operation, from 45 to 75 per cent of the blood pumped into the aorta was short-circuited into the pulmonary artery. The authors discuss in detail the roentgenographic signs observed in patients with patent ductus arteriosus and find that while these signs may not be sufficient to establish the diagnosis definitely, they often contribute important confirmatory evidence and bear witness as to the effectiveness of therapy.

Touroff and Vesell [28] have reported their results in the surgical treatment of subacute bacterial endarteritis complicating patent ductus arteriosus. Of 4 patients operated on, 2 died of hemorrhage at operation, 1 died of subacute bacterial endarteritis thirty-two weeks after operation and 1 improved and was in "excellent condition" thirty-six weeks after operation. This marks the first successful treatment of subacute bacterial endarteritis by surgical means, and the achievement justifies further attempts.

RHEUMATIC HEART DISEASE

There have been a number of interesting reports [29] on different aspects of the rheumatic fever problem, but none are of outstanding importance.

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28. Touroff, A. S. W., and Vesell, H.: Experiences in the Surgical Treatment of Subacute Streptococcus Viridans Endarteritis Complicating Patent Ductus Arteriosus, J. Thoracic Surg. **10**:59, 1940; Subacute Streptococcus Viridans Endarteritis Complicating Patent Ductus Arteriosus: Recovery Following Surgical Treatment, J. A. M. A. **115**:1270 (Oct. 12) 1940.

29. Thomson, S., and Innes, J.: Haemolytic Streptococci in the Cardiac Lesions of Acute Rheumatism, Brit. M. J. **2**:733, 1940. Stone, S.: Treatment of Sydenham's Chorea by Fever and Vitamin B Therapy, New England J. Med. **223**:489, 1940. Hedley, O. F.: Rheumatic Heart Disease in Philadelphia Hospitals: Study of 4,653 Cases of Rheumatic Heart Disease, Rheumatic Fever, Sydenham's Chorea and Subacute Bacterial Endocarditis Involving 5,921 Admissions to Philadelphia Hospitals from January 1, 1930, to December 1, 1934; III. Fatal Rheumatic Heart Disease and Subacute Bacterial Endocarditis, Pub. Health Rep. **55**:1707, 1940. Altschule, M. D., and Budnitz, E.: Rheumatic Disease of the Tricuspid Valve, Arch. Path. **30**:7 (July) 1940. Stroud, W. D., and Twaddle, P. H.: Fifteen Years' Observation of Children with Rheumatic Heart Disease, J. A. M. A. **114**: 629 (Feb. 24) 1940. Klein, R. I.; Levinson, S. A., and Rosenblum, P.: Weltmann Reaction and Sedimentation Rate During Rheumatic Fever of Childhood, Am. J. Dis. Child. **59**:48 (Jan.) 1940. Walsh, B. J.; Bland, E. F., and Jones, T. D.: Pure Mitral Stenosis in Young Persons, Arch. Int. Med. **65**:321 (Feb.) 1940. Sosman, M. C.: Subclinical Mitral Disease, J. A. M. A. **115**:1061 (Sept. 28)

Wasson and Brown [30] have again reported encouraging results following inoculation of hemolytic streptococcus filtrate into patients with rheumatic fever. Five and nine-tenths per cent of the original group of 43 patients treated over a period of four years suffered attacks of acute rheumatic fever with or without carditis, whereas the two control groups observed during the same period showed an incidence of 15 and 43.4 per cent, respectively. A second group of 32 patients was immunized over a two year period. During the first year of treatment attacks of acute rheumatic fever, carditis and chorea developed in 9.4 per cent, as compared with 44 per cent in the control group. During the second year the incidence of rheumatic fever in the treated group (31 patients) was only 3.2 per cent, while in a new control group the incidence was 28 per cent. Wasson and Brown, encouraged by these results, are planning more comprehensive studies for the future. It is to be hoped that, in addition to treating larger numbers of patients, a better method of selecting controls will be used. Both the treated and the control groups should be similar in all respects, and neither patient nor parent should know whether hemolytic streptococcus filtrate or physiologic solution of sodium chloride is being given.

Coburn and Moore have further reported [31] on the prolonged prophylactic use of sulfanilamide in treating rheumatic fever. One gram of the drug was given three times daily to large children and twice daily to small children over a period of nine months. Interestingly enough, in the 10 per cent in whom toxic effects developed, symptoms always appeared within the first two weeks. In those who tolerated the sulfanilamide during this period signs of toxicity did not develop later on. Infections of the throat caused by hemolytic streptococci developed in only 3 per cent of 184 treated children, and rheumatic fever occurred in only 1 case. In the untreated children the incidence of streptococcic infections of the throat was about 50 per cent, and the incidence of attacks of rheumatic fever was 20 per cent in one group and 30 per cent in another. These

1940. Boas, E. P., and Ellenberg, M.: Rheumatic Pericarditis with Effusion Treated with Salicylates, ibid. **115**:345 (Aug. 3) 1940. Brown, M. G., and Wolff, L.: Recovery from Acute Rheumatic Fever Without Permanent Cardiac Damage, New England J. Med. **223**:242, 1940. Bennett, G. A.; Zeller, J. W., and Bauer, W.: Subcutaneous Nodules of Rheumatoid Arthritis and Rheumatic Fever, Arch. Path. **30**:70 (July) 1940. Swift, H. F.: Rheumatic Heart Disease, Pathogenesis and Etiology in Their Relation to Therapy and Prophylaxis, Medicine **19**:417, 1940.

30. Wasson, V. P., and Brown, E. E.: Immunization Against Rheumatic Fever with Hemolytic Streptococcus Filtrate, Am. Heart J. **20**:1, 1940.

31. Coburn, A. F., and Moore, L. V.: The Prophylactic Use of Sulfanilamide in Rheumatic Subjects, M. Clin. North America **24**:633, 1940.

results are in accord with those previously reported [32] and not only suggest a means of preventing the exacerbations of rheumatic fever but afford additional evidence of the close association between this disease and streptococcic pharyngitis. If the good results obtained by Coburn and Moore and others are substantiated by further trial, the only question remaining is that of the possible harmful effects of prolonged administration of sulfanilamide. The answer to this question will probably appear as a corollary to the answer to the main problem.

BACTERIAL ENDOCARDITIS

Chemotherapy alone or in combination with some other therapeutic measure [33] has now been tried in a large number of cases of subacute bacterial endocarditis. The results, in our opinion, are definitely encouraging, in view of the heretofore hopeless prognosis. Lichtman and Bierman [34] have reviewed the published reports in an effort to arrive at a tentative conclusion as to which method of treatment at present offers the greatest hope for recovery. They have analyzed the cases of 287 adequately treated patients. Of a total of 198 patients treated with sulfanilamide and its derivatives, recovery occurred in 12, or 6 per cent. Although most of the 198 patients received sulfanilamide, the preference at this time is for sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine). Favorable results have not been obtained with sulfathiazole (2-[paraaminobenzene] thiazole) when the endocarditis has been due to Streptococcus viridans. Of a total of 43 patients receiving chemotherapy and heparin, 5, or 11.5 per cent, have recovered. Of 25 patients subjected to chemotherapy and hyperthermia, 4, or 16 per cent, have recovered, and in a series of 21 patients who were given intravenous injections of typhoid-paratyphoid vaccine to induce pyrexia, 5, or 25 per cent, recovered. Among 6 additional patients receiving chemotherapy and radiotherapy there were no recoveries. Lichtman and Bierman conclude that the incidence of recovery from subacute bacterial endocarditis when chemotherapy is combined with additional forms of treatment, such as use of heparin and induction of hyperthermia, is twice as good as when sulfanilamide or one of its derivatives is employed alone. It would also appear that the combined use of intravenous injections of typhoid-paratyphoid vaccine and chemotherapy deserves especial mention and further trial.

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32. Thomas, C. B., and France, R.: A Preliminary Report of the Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, Bull. Johns Hopkins Hosp. **64**:67, 1939.

33. Bierman, W., and Baehr, G.: The Use of Physically Induced Pyrexia and Chemotherapy in the Treatment of Subacute Bacterial Endocarditis, J. A. M. A. **116**:292 (Jan. 25) 1941.

34. Lichtman, S. S., and Bierman, W.: The Treatment of Subacute Bacterial Endocarditis: Present Status, J. A. M. A. **116**:286 (Jan. 25) 1941.

Osgood [35] also reports a few favorable results following the intensive use of neoarsphenamine, but others have not as yet reported similar success.

With regard to chemotherapy for subacute bacterial endocarditis, it appears that if the initial response to the drug is not favorable the likelihood of cure is negligible. Exceptionally, it has been noted that if the response to sulfapyridine is poor or if so-called sulfapyridine fastness results, a change to sulfanilamide or sulfathiazole may be worth while. This great variability in response, wherein the symptoms and fever disappear and the blood stream is sterilized in one case and not in another, suggests that the various strains of Str. viridans respond differently to the drugs used. This is illustrated nicely by the observations of Swain.[36] He compared the action of these drugs clinically with that on the same organism in vitro. In 2 cases in which response was poor or there was none at all the streptococci obtained on culture grew freely in broth containing the drugs. In 2 other cases in which there was a favorable response to treatment, the growth of streptococci obtained on culture was inhibited by low concentration of the drug. Here, obviously, is a good line of attack. It not only provides a plausible explanation for the small number of cures but suggests the necessity for the proper selection of cases. If most strains of Str. viridans are resistant to the drugs known at present it should encourage the preparation of related compounds which may prove more effective.

Bacterial endocarditis complicating syphilitic disease of the aortic valve has heretofore been regarded as a rare anomaly. It is, therefore, somewhat surprising to have for review three papers published on this subject during the past year.[37] It would appear that bacterial endocarditis may be associated with syphilitic disease of the aorta alone or with syphilitic involvement of the cusps and commissures of the aortic valves. The diagnosis is usually difficult but may be suspected when, in the presence of syphilitic aortic insufficiency, there occur the intermittent fever and the secondary anemia which so often characterize subacute bacterial endocarditis.

EXPERIMENTAL RENAL HYPERTENSION

It has been increasingly difficult to keep abreast of the many investigations dealing with experimental arterial hypertension, and reference

35. Osgood, E. E.: Personal communication to the reviewers.

36. Swain, R. H. A.: Strain Variations in the Resistance of Streptococcus Viridans to Sulphonamide Compounds, Brit. M. J. **1**:722, 1940.

37. Rosenberg, D. H.: Bacterial Endocarditis and Syphilis of the Aortic Valve, Arch. Int. Med. **66**:441 (Aug.) 1940. Boyd, C. H.: Bacterial Endocarditis and Syphilitic Heart Disease, Rhode Island M. J. **23**:47, 1940. Braunstein, A. L., and Townsend, S. R.: Bacterial Endocarditis Superimposed on Syphilitic Aortic Valvulitis, Arch. Int. Med. **65**:957 (May) 1940.

should be made to recent reviews [38] for comprehensive and detailed reports. The investigations so far have conclusively demonstrated a direct relationship between renal ischemia and hypertension in laboratory animals. Furthermore, there is growing evidence of similarity between this form of experimental hypertension and essential hypertension. And, finally, the culmination of this work is seen in the carefully worded, yet none the less dramatic, announcements of the successful treatment of experimental hypertension in animals and of hypertension in man by the use of kidney extracts.

The Mechanism of Renal Hypertension.—Investigations continue to center around renin, the protein-like pressor substance of the kidney.[39] It has now been shown that renin may be produced by the completely, as well as the partially, ischemic kidney.[40] The experiments of Kohlstaedt and Page [41] provide a clue to the reason clamping the renal artery is effective in producing hypertension. Isolated dog's kidneys were perfused with defibrinated blood under various hemodynamic conditions. Venous blood from the perfused kidney was tested for renin by addition of renin activator and observation of its pressor effect on the vessels of the isolated rabbit's ear. It was found that renin was not secreted by the kidney during normal pulsate perfusion but that it was secreted when the pulse pressure was reduced by partially clamping the renal

38. Blalock, A.: Experimental Hypertension, Physiol. Rev. **20**:159, 1940. Page, I. H.: Newer Aspects of Experimental Hypertension, Publication 13, American Association for the Advancement of Science, 1940, p. 239. Goldblatt, H.: Studies on Experimental Hypertension: XII. The Experimental Production and Pathogenesis of Hypertension Due to Renal Ischemia, Am. J. Clin. Path. **10**:40, 1940.

39. Battro, A.; Braun-Menendez, E.; Lanari, A., and Leloir, L. F.: Acción presora en el hombre de la renina y de la hipertensina, Rev. Soc. argent. de biol. **16**:376, 1940. Blalock, A.; Levy, S. E., and Cressman, R. D.: Experimental Hypertension: The Effects of Unilateral Renal Ischemia Combined with Intestinal Ischemia on the Arterial Blood Pressure, J. Exper. Med. **69**:833, 1939. Taggart, J., and Drury, D. R.: The Action of Renin on Rabbits with Renal Hypertension, ibid. **71**:857, 1940. Corcoran, A. C., and Page, I. H.: The Effects of Angiotonin on Renal Blood Flow and Glomerular Filtration, Am. J. Physiol. **130**:335, 1940. Gerbi, C.; Rubenstein, B. B., and Goldblatt, H.: Studies on Experimental Hypertension: X. The Oxygen Consumption of the Ischemic Kidney, J. Exper. Med. **71**: 71, 1940.

40. Taquini, A. C.: The Production of a Pressor Substance by the Totally Ischemic Kidney, Am. Heart J. **19**:513, 1940. Prinzmetal, M.; Lewis, H. A., and Leo, S. D.: The Etiology of Hypertension Due to Complete Renal Ischemia, J. Exper. Med. **72**:763, 1940. Leo, S. D.; Prinzmetal, M., and Lewis, H. A.: Observations upon the Pressor Substance Causing the Rise in Blood Pressure Following the Termination of Temporary Complete Renal Ischemia, Am. J. Physiol. **131**:18, 1940.

41. Kohlstaedt, K. G., and Page, I. H.: Liberation of Renin by Perfusion of Kidneys Following Reduction of Pulse Pressure, J. Exper. Med. **72**:201, 1940.

artery. Under these conditions the secretion of renin was not prevented by increasing the rate of flow or pressure of the perfusate. The authors concluded that the change from normal pulsate to continuous flow, following the clamping of the renal artery, leads to edema and anoxia of the cells of the tubules. This, in turn, increases permeability of the cellular membrane and allows the liberation of the large renin molecule.

Apparently, renin requires the presence of another substance, normally present in plasma, before its full pressor effect is manifested. Muñoz and his associates [42] regard renin as an enzyme which acts on a blood globulin, hypertensin precursor, and gives rise to a substance, hypertensin, which has a direct vasoconstrictor action. They also describe another enzyme, hypertensinase, which destroys hypertensin and is present in blood and tissues. Page and his associates,[43] also, believe that renin is an enzyme which reacts with renin activator to produce a pressor substance, angiotonin. Angiotonin does not exert its vasoconstrictor effect in the absence of a substance contained in red blood cells, which has been termed angiotonin activator. Repeated injections of angiotonin lead to gradual lessening of the pressor response, which, Page believes, is due not only to exhaustion of the activating substance but to the development of inhibitor substances. That these inhibitors originate in large part in the kidneys is apparently shown by the increased sensitivity to angiotonin following bilateral nephrectomy.

At this point it is of interest to mention the results of some experiments carried out by Dock.[44] He found that on pithing the central nervous system of rabbits with renal hypertension there is a rapid fall of blood pressure to as low a level as that of normal controls. A rise in arterial pressure was easily evoked with epinephrine or with renin. From this it is argued that renin must, therefore, differ from the humoral agent causing chronic hypertension. Furthermore, it was found that pithed hypertensive animals are much more sensitive than pithed control animals, although in the former sensitivity was lost within thirty hours after removal of the kidney which had caused the hypertension. Dock concludes that the nervous system is as important in maintaining hypertension as it is in maintaining normal pressure levels and that the humoral

42. Muñoz, J. M.; Braun-Menendez, E.; Fasciolo, J. C., and Leloir, L. F.: The Mechanism of Renal Hypertension, Am. J. M. Sc. **200**:608, 1940.

43. Page, I. H., and Helmer, O. M.: Angiotonin-Activator, Renin- and Angiotonin-Inhibitor, and the Mechanism of Angiotonin Tachyphylaxis in Normal, Hypertensive, and Nephrectomized Animals, J. Exper. Med. **71**:495, 1940. Kohlstaedt, K. G.; Page, I. H., and Helmer, O. M.: The Activation of Renin by Blood, Am. Heart J. **19**:92, 1940. Page, I. H., and Helmer, O. M.: A Crystalline Pressor Substance (Angiotonin) Resulting from the Reaction Between Renin and Renin-Activator, J. Exper. Med. **71**:29, 1940.

44. Dock, W.: Vasoconstriction in Renal Hypertension Abolished by Pithing, Am. J. Physiol. **130**:1, 1940.

agent in renal hypertension may act by increasing the sensitivity to epinephrine and to stimuli of vasomotor nerves and by modifying the " 'set' of the vasomotor mechanism," just as substances from inflamed or necrotic tissue modify the set of the heat-regulating center. Thus, both a humoral and a nervous mechanism are postulated as causative and maintaining factors in renal hypertension.

That the normal kidney in some manner limits the pressor effect in experimental hypertension has been shown by several investigators. More recently it has been shown that extracts of kidney (and of muscle) reduce the blood pressure in experimental renal hypertension and in essential and malignant hypertension in man.

Harrison, Grollman and Williams [45] have prepared a kidney extract which is effective in lowering the blood pressure in hypertensive rats, dogs and human subjects. The extract is prepared only with great difficulty, and, though the chemical nature of the active principle is unknown, it has certain unique properties which differentiate it from various depressor tissue extractives previously described. The extract was given orally or parenterally to a few patients with advanced and severe hypertension. In most of the subjects there were a decline in the blood pressure and subjective improvement, but the authors prefer to regard the studies on patients as inconclusive and still in the experimental stage.

Page and his associates [46] write with greater assurance. They prepared extracts from fresh kidneys and other tissues, chiefly muscle. Each of the 8 patients who received these extracts responded with "a sharp prolonged fall in arterial pressure," whether the hypertension was malignant or essential. Associated with the fall in blood pressure was marked improvement. Three to five days after the treatment was discontinued the blood pressure tended to rise again. Page and associates point out that there is little likelihood that the fall in blood pressure could be due to any of the known depressor substances, for three reasons. First, the fall occurs slowly—over a period of twelve to forty-eight hours—depending on dosage. Second, all crystalloidal substances would have been lost during dialysis, for the inhibitor is nondialyzable. Third, the reduction

45. Harrison, T. R.; Grollman, A., and Williams, J. R., Jr.: The Anti-Pressor Action of Renal Extracts and Their Capacity to Reduce the Blood Pressure of Hypertensive Rats, Am. J. Physiol. **128**:716, 1940. Williams, J. R., Jr.; Grollman, A., and Harrison, T. R.: The Reduction of the Blood Pressure of Hypertensive Dogs by the Administration of Renal Extract, ibid. **130**:496, 1940. Grollman, A.; Williams, J. R., Jr., and Harrison, T. R.: Reduction of Elevated Blood Pressure by Administration of Renal Extracts, J. A. M. A. **115**:1169 (Oct. 5) 1940.

46. Page, I. H.; Helmer, O. M.; Kohlstaedt, K. G.; Fouts, P. J.; Kempf, G. F., and Corcoran, A. C.: Substance in Kidneys and Muscle Eliciting Prolonged Reduction of Blood Pressure in Human and Experimental Hypertension, Proc. Soc. Exper. Biol. & Med. **43**:722, 1940.

in pressure remains for several days, in contradistinction to the transient reduction resulting from injection of histamine, choline, adenylic acid, etc.

Various drugs and extracts [47] have been tested in regard to their effect on the blood pressure of rats and dogs with renal hypertension. None save renal extracts had an appreciable effect in lowering the blood pressure, and the clinical value of so-called depressor substances is thus questionable. The administration of relatively large doses of sodium chloride did not markedly elevate the blood pressure.

Essential Hypertension.—Last year we reviewed [48] in detail an article by Robinson and Brucer [49] on the range of normal blood pressure. The validity of any conclusion which was based on their statistical method has been called into question by Treloar.[50] The conclusions presented by Robinson and Brucer are of such importance that an effort should be made to lift them above all possible criticism or to alter them if found incorrect.

Robinson and his associates have continued their interesting studies on blood pressure. Hypotension [51] (blood pressure below 110 systolic and 70 diastolic) is regarded not as a disease but as an ideal blood pressure level. In regard to body build,[52] it was found that persons of linear (narrow-chested) build had lower blood pressures than persons of lateral (broad-chested) build and that hypertension tended to develop less frequently in the former. Because of this positive correlation the authors regard the hereditary predisposition to normal pressure and to hypertension as an established fact. In regard to obesity,[53] it was found that there was a steplike rise in blood pressures with an increase in ponderal index (weight divided by height) toward obesity. It is pointed out that the significance of this fact must be withheld until the influence of body build on obesity has been appraised.

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47. Grollman, A.; Harrison, T. R., and Williams, J. R., Jr.: Therapeutics of Experimental Hypertension, J. Pharmacol. & Exper. Therap. **69**:76, 1940. Wakerlin, G. E., and Gaines, W.: The Effect of Various Agents on the Blood Pressure of Renal Hypertensive Dogs, Am. J. Physiol. **130**:568, 1940.

48. Graybiel, A., and White, P. D.: Diseases of the Heart: A Review of Significant Contributions Made During 1939, Arch. Int. Med. **65**:1053 (May) 1940.

49. Robinson, S. C., and Brucer, M.: Range of Normal Blood Pressure: A Statistical and Clinical Study of 11,383 Persons, Arch. Int. Med. **64**:409 (Sept.) 1939.

50. Treloar, A. E.: Normal Blood Pressure, Arch. Int. Med. **66**:848 (Oct.) 1940.

51. Robinson, S. C.: Hypotension: The Ideal Normal Blood Pressure, New England J. Med. **223**:407, 1940. Treloar.[50]

52. Robinson, S. C., and Brucer, M.: Body Build and Hypertension, Arch. Int. Med. **66**:393 (Aug.) 1940.

53. Robinson, S. C.; Brucer, M., and Mass, J.: Hypertension and Obesity: Statistical and Clinical Study of 10,883 Individuals, J. Lab. & Clin. Med. **25**:807, 1940.

The surgical treatment of hypertension by means of bilateral splanchnicectomy continues to be favorably reported on.[54] De Takáts and Scupham [55] decapsulated the kidneys and wrapped omentum or a pedicled muscle flap around those organs in 4 cases of hypertension with malignant nephrosclerosis. There was no definite improvement in any case.

There have been a number of reports [56] in regard to the association of hypertension and disease of the kidneys. The general conclusion is reached that only an occasional patient is benefited by removal of the diseased kidney and that removal should be for reasons other than the relief of hypertension.

CORONARY HEART DISEASE

Blumgart, Schlesinger and Davis [57] have described in great detail a joint clinical and pathologic study of autopsy records of 125 consecutive cases in which clinical manifestations of angina pectoris, coronary thrombosis, myocardial infarction and congestive failure were related to pathologic changes observed in the coronary arteries and in the heart muscle. Thirty cases representing all the patients with clinical evidence of car-

54. Peet, M. M.; Woods, W. W., and Braden, S.: The Surgical Treatment of Hypertension: Results in Three Hundred and Fifty Consecutive Cases Treated by Bilateral Supradiaphragmatic Splanchnicectomy and Lower Dorsal Ganglionectomy, J. A. M. A. **115**:1875 (Nov. 30) 1940. Allen, E. V., and Adson, A. W.: The Treatment of Hypertension: Medical Versus Surgical, Ann. Int. Med. **14**:288, 1940.

55. de Takáts, G., and Scupham, G. W.: Revascularization of the Ischemic Kidney, Arch. Surg. **41**:1394 (Dec.) 1940.

56. Crabtree, E. G.; Pyelonephritic Injuries to the Kidney and Their Relation to Hypertension, J. Urol. **44**:125, 1940. Barker, N. W., and Walters, W.: Hypertension and Chronic Atrophic Pyelonephritis: Results of Nephrectomy, J. A. M. A. **115**:912 (Sept. 14) 1940. Nesbit, R. M., and Ratliff, R. K.: Hypertension Associated with Unilateral Renal Disease, ibid. **116**:194 (Jan. 18) 1941. Palmer, R. S.; Chute, R.; Crone, N. L., and Castleman, B.: The Renal Factor in Continued Arterial Hypertension Not Due to Glomerulonephritis as Revealed by Intravenous Pyelography: A Study of Two Hundred and Twelve Cases, with a Report of the Results of Nephrectomy in Nine Cases, New England J. Med. **223**: 165, 1940. Schroeder, H. A., and Fish, G. W.: Studies on "Essential" Hypertension: III. The Effect of Nephrectomy upon Hypertension Associated with Organic Renal Disease, Am. J. M. Sc. **199**:601, 1940. Braasch, W. F., and Jacobson, C. E.: Chronic Bilateral Pyelonephritis, J. Urol. **44**:571, 1940. Braasch, W. F.; Walters, W., and Hammer, H. J.: Hypertension and the Surgical Kidney, J. A. M. A. **115**:1838 (Nov. 30) 1940. Crabtree, E. G., and Chaset, N.: Vascular Nephritis and Hypertension: A Combined Clinical and Clinicopathologic Study of One Hundred and Fifty Nephrectomized Patients, ibid. **115**:1842 (Nov. 30) 1940.

57. Blumgart, H. L.; Schlesinger, M. J., and Davis, D.: Studies on the Relation of the Clinical Manifestations of Angina Pectoris, Coronary Thrombosis, and Myocardial Infarction to the Pathologic Findings, with Particular Reference to the Significance of the Collateral Circulation, Am. Heart J. **19**:1, 1940.

diac pain or congestive failure or with anatomic evidence of coronary occlusions were compared with the remaining 95 cases. The authors' chief conclusions, in part, are as follows:

In normal hearts, intercoronary anastomoses larger than 40 micra in diameter are not found.

Obstruction to normal coronary arterial blood flow by arteriosclerotic narrowing or occlusion regularly results in the development of intercoronary anastomoses measuring 40 to 200 micra in diameter.

Such anastomotic circulation may so well compensate for occlusion or marked narrowing of a major coronary artery that the blood supply to the heart remains adequate for the ordinary activities of life. When the narrowing or occlusion progresses so far that the coronary circulation is insufficient to meet the needs of the heart during periods of increased work, myocardial anoxemia results. The "coronary reserve" is clearly reduced. The frequency of angina pectoris in patients who show such pathologic changes is in accord with these considerations.

The pathologic basis for congestive failure in patients with coronary arterial disease or angina pectoris was studied. The results suggest that constantly undernourished areas in hearts which are the seat of coronary arteriosclerosis, when subjected to still greater anoxemia, such as is brought about by exertion or emotion, undergo focal necrosis and a diffuse fibrous change. The replacement by connective tissue leads to myocardial weakness and congestive failure. The hearts with the greatest amount of replacement of myocardial fibers by fibrous tissue were found in patients who, after some months or years of angina pectoris, finally developed congestive failure.

A comparative study of the clinical characteristics of coronary thrombosis and those of myocardial infarction forces the conclusion that coronary thrombosis and occlusion, per se, do not necessarily produce any characteristic clinical manifestations. If an occlusion occurs gradually, over months or years, with the concomitant development of an anastomotic circulation, no symptoms or signs will be produced and no myocardial lesions will be demonstrable.

The syndrome usually called "coronary occlusion," which consists of prolonged substernal oppression or pain, a fall in blood pressure, pallor, and other manifestations of shock, and is accompanied by electrocardiographic changes, fever, leucocytosis, and an increased sedimentation rate, in reality signifies myocardial infarction, and should be so termed.

Attacks of severe, prolonged pain, associated at times with collapse, evidently result from prolonged insufficiency of the blood supply to the myocardium and consequent anoxia. This "coronary failure" may occur with or without simultaneous, or immediately preceding, coronary thrombosis.

If such "coronary failure" is sufficiently prolonged, myocardial infarction results. This may be obviated in some instances, however, if the demands on the myocardium are quickly reduced by rest in bed, sedatives, or the control of rapid ventricular rates.

In the hearts of several patients in which the coronary blood flow was already reduced and presumably slowed because of occlusions and narrowing, the sudden fall in blood pressure which accompanied postoperative shock evidently led to further stagnation, anoxemia, and the deposition of multiple coronary thrombi. The importance of avoiding a fall in blood pressure, whatever the cause, in cases of coronary arteriosclerosis is emphasized.

Anoxia, necrosis, infarction, and fibrosis of the myocardium, and their accompanying clinical manifestations, arise whenever there is a discrepancy between the nutritional requirements of the heart muscle, on the one hand, and the factors governing nutritional supply, on the other. The extraordinary significance of the collateral circulation in bridging the discrepancy between supply and demand is emphasized.

Fauteux [58] has described a new surgical procedure for the treatment of coronary arteriosclerosis. He points out that one of the fundamental principles in surgical treatment of peripheral vascular disorders is the desirability of ligating the companion vein whenever a major artery is ligated or diseased. The beneficial effect of this procedure is brought about by maintaining within the limb for a longer period the smaller amount of blood supplied by the collateral circulation. Fauteux applied this method in experiments on the dog's heart. He found that whereas resection of a portion of the ramus descendens of the left coronary artery was almost always fatal, if the companion vein was ligated at the same time the dogs survived. Even when the arterial resection was carried out months after the ligation of the vein the animals survived. These results suggested that "in cases properly selected coronary vein ligation may be expected to act as a preventive measure against a second attack of coronary thrombosis and also to improve the coronary circulation sufficiently to relieve the pain of 'angina of effort.'"

Raab [59] has reported his results on the treatment of 100 patients with angina pectoris by means of roentgen irradiation of the adrenal glands. Symptoms were relieved in 76 of the 100. Of the 76, 62 "were entirely or almost entirely freed from complaints or, at least, considerably improved" for an average period of thirteen and one-half months, and the remaining 14 were moderately improved during an average period of seven and a half months. We are frankly skeptical of these results, having used a similar procedure in a small number of cases without success.

TREATMENT OF HEART FAILURE

Although galenic preparations of digitalis have enjoyed widespread preference among physicians in this country, intense interest has been maintained in the purified glucosides of this drug. It has long been the ambition of some investigators to isolate all the glucosides of digitalis, explore the therapeutic possibilities of each separately and then synthetically regroup them in order to reconstruct the global effect of the drug. Recent studies have emphasized the importance and therapeutic

58. Fauteux, M.: Experimental Study of the Surgical Treatment of Coronary Disease, Surg., Gynec. & Obst. **71**:151, 1940.

59. Raab, W.: Roentgen Treatment of the Adrenal Glands in Angina Pectoris (One Hundred Cases), Ann. Int. Med. **14**:688, 1940.

value of lanatosid C. ($C_{49}H_{76}O_{20}$).[60] Kwit, Gold and Cattell[60b] have observed that lanatosid C compared favorably with digitalis leaf in a study of a selected group of 67 patients, some with auricular fibrillation and others with regular sinus rhythm. Fahr and La Due[60c] found this glucoside to be as effective therapeutically in cases of heart failure with normal rhythm as in cases of auricular fibrillation. Kwit and associates observed that the range between the therapeutic dose and the toxic dose for lanatosid C in man is similar to that for the digitalis leaf but that the former is not rapidly absorbed, since it requires many times the intravenous dose to cause similar effects by oral administration. The full digitalizing dose of lanatosid C by intravenous injection is about 1.5 mg. (6 cat units) given within two to three hours. The desirability of such a preparation which may not require bioassay is readily apparent.

MISCELLANEOUS

Kinked Carotid Artery.—Parkinson, Bedford and Almond[61] have described the so-called kinked carotid artery on the basis of 47 of their own cases and a review of those previously published. The common form of kinked carotid artery is generally associated with hypertension or with arteriosclerosis or with the two in combination and occurs in elderly women, especially those with spinal curvature and obesity; it is scarcely ever seen in men. The swelling consists of an arterial prominence in the region of the bifurcation of the innominate artery and may be formed by a loop of the right carotid artery, though the innominate and the subclavian artery may contribute. There are no symptoms beyond local throbbing, and prognosis is not adversely affected.

Gonorrheal Myocarditis.—Bang[62] has attempted to show that gonorrheal myocarditis may be a fairly frequent complication of gonococcic infection, having observed 6 cases in the course of one year in a medical ward. The diagnosis was made chiefly on the basis of electrocardiographic changes developing during the course of complicated gonorrhea. He further suggests that while in some cases the myocarditis is slight and transitory, in others it may lead to chronic degenerative heart disease.

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60. (*a*) Kaplan, J. J., and Visscher, M. B.: Comparative Toxicity Studies of the Glucosides of Digitalis Lanata in the Pigeon, Cat and Dog, with Some Observations on the Influence of Anesthesia, J. Pharmacol. & Exper. Therap. **70**:228, 1940. (*b*) Kwit, N. T.; Gold, H., and Cattell, M.: Studies on Purified Digitalis Glucosides: II. Potency and Dosage of Lanatoside C in Man, ibid. **70**:254, 1940. (*c*) Fahr, G. E., and La Due, J. S.: Personal communication to J. J. Kaplan and M. B. Visscher, 1940.

61. Parkinson, J.; Bedford, D. E., and Almond, S.: The Kinked Carotid Artery That Simulates Aneurysm, Brit. Heart J. **1**:345, 1939.

62. Bang, O.: Gonorrheal Myocarditis, Brit. M. J. **1**:117, 1940.

We are of the opinion that the latter conclusion is not established by the available data and is, moreover, unlikely to prove true.

Pulmonary Embolism.—Pulmonary embolism is of particular interest to cardiologists because it may simulate or complicate heart disease. Recent studies [63] have added to knowledge of this disorder. White points out [63d] that pulmonary embolism frequently goes unrecognized and that its detection will often explain obscure signs and symptoms, refractoriness to treatment and periodic episodes of fever, tachycardia or collapse. That consideration be given to the following clues to the diagnosis of obscure pulmonary embolism is recommended by White and other authors: (1) the occurrence of unexplained fever, leukocytosis, tachycardia, faintness, prostration, dyspnea, asthma or even jaundice (from hemolysis of a large infarct plus an engorged liver), especially in a patient with heart disease (particularly in the presence of mitral stenosis or heart failure); (2) the finding of pulmonary signs (rales or consolidation) not adequately explained by either congestive heart failure or pulmonary infection; (3) the periodic recurrence at short intervals of episodes that individually might be mistaken for acute coronary occlusion but which in series are much more likely to mean repeated pulmonary embolism; (4) the inexplicable lack of response in a case of congestive heart failure to therapy which seemingly should be adequate (other factors, such as infection, infarction elsewhere than in the lungs and thyrotoxicosis being ruled out), and (5) in a few cases, the occurrence of the electrocardiogram characteristic of acute cor pulmonale (prominent S waves in lead I; low, flat or even inverted T waves in lead II; prominent Q waves and inverted T waves in lead III, and low, flat or inverted T waves in lead IV) when the right ventricle is dilated by a massive embolism (not, therefore, in the majority of cases of pulmonary embolism) and simulating at first glance the electrocardiogram of acute coronary thrombosis with basal infarction.

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63. (*a*) Parsons-Smith, B.: Pulmonary Embolism and Infarction, Brit. M. J. **2**:179, 1940. (*b*) Stewart, H. J.; Kirk, R. C., and Smith, J. J.: Electrocardiographic Changes in Pulmonary Infarction, Internat. Clin. **3**:135, 1940. (*c*) Sokolow, M.; Katz, L. N., and Muscovitz, A. N.: The Electrocardiogram in Pulmonary Embolism, Am. Heart J. **19**:166, 1940. (*d*) White, P. D.: Pulmonary Embolism and Heart Disease: A Review of Twenty Years of Personal Experience, Am. J. M. Sc. **200**:577, 1940.

News and Comment

Directory of Medical Specialists.—A second edition of the Directory of Medical Specialists has been authorized by the Advisory Board for Medical Specialties, to be ready for distribution in February 1942, with its contents complete to January 1. This directory, the official publication of the Advisory Board, will list the names of approximately 18,000 diplomates of the fifteen American boards examining candidates for certification in the specialties. This number is an increase of 4,000 over those listed in the first edition, issued early in 1940. The geographic grouping will give completely revised biographic data about each diplomate; there will be an alphabetic index, with addresses and specialty designations, and a full outline of the plan of organization, the officers and the examination requirements of each American board.

Information not found in the first edition will be included in the second, such as details of formal training and military appointments.

All who have been formally certified by one of the American boards will be included.

The publication is issued through the Columbia University Press, New York. The secretary of each specialty board serves on the Advisory Editorial Board, and Dr. Paul Titus, 1015 Highland Building, Pittsburgh, of the American Board of Obstetrics and Gynecology, is the directing editor.

1941 Graduate Fortnight of the New York Academy of Medicine.—The New York Academy of Medicine will hold a Graduate Fortnight Oct. 13-24, 1941. The subject for discussion will be "Cardiovascular Diseases, Including Hypertension."

Members of the medical profession are eligible for registration.

A complete program and registration blank may be secured by addressing Dr. Mahlon Ashford, 2 East One Hundred and Third Street, New York.

Book Reviews

Applied Pharmacology. By Hugh Alister McGuigan, Ph.D., M.D., F.A.C.P., Professor of Pharmacology and Therapeutics, University of Illinois College of Medicine. Price, $9. Pp. 914. St. Louis: C. V. Mosby Company, 1940.

The title of this book is misleading. It is not in any sense a manual of therapeutics, nor is it a discussion of the modification of physiologic processes such as that given in the text by Clark, published under this same title since 1923. While there is no reference in the preface to the author's earlier text "Pharmacology and Therapeutics" (1928), the two follow the same general plan, and at least part of the newer volume has been taken bodily from the older.

The factual material of pharmacology has come to be so extensive that the chief problem of those who are responsible for presenting it either in classroom or text is one of selection. There is compiled a tremendous amount of information in the volume under consideration. Each drug is discussed after the conventional pattern, i. e., members of its group, chemistry, pharmacodynamics, toxicology, therapeutic uses, preparations, etc. A considerable amount of review of physiologic mechanisms is scattered throughout the text, sometimes in relation to the context. However, the reviewer feels that the book lacks a broad plan and that there is therefore considerable disorganization. Although there are no divisions into numbered chapters with appropriate titles, both the table of contents and the size of type and placing of headings indicate, or should indicate, the subdivision of material. Actually, this subdivision often follows no recognizable pattern. For example, functions of the stomach, hypersecretion and peptic ulcer are discussed under "Deglutition." Thiocyanates are considered under "The Reticuloendothelial System." Perhaps worst of all, not only are radium, lead, iron and aluminum listed under "The Chemotherapy of Syphilis," but the running title for each page of discussion of these subjects is also "Chemotherapy of Syphilis."

In a book of this length a reviewer must be content with samples taken at random. Such samples reveal some serious errors of fact. The solution of posterior pituitary U. S. P. is said to be standardized by comparison with histamine. It is true that the assay introduced into the Pharmacopeia of the United States IX was based on this comparison, but this method has not been official since Jan. 1, 1926. It is always an error to refer to a commercial preparation with a distinctive trade name as an internal secretion. "At least two internal secretions (pitressin and cortin) have a definite effect on the secretion of the urine" (page 389). According to the author's own statement (page 853), pitressin "is an aqueous preparation of the posterior lobe containing 20 units of the pressor principle . . . per cubic centimeter. . . Five-tenths per cent chlorbutanol is used as a preservative." The author is not the only one to fall into this error.

Although many structural formulas are given, it is rather surprising to find that for morphine omitted, especially in view of the large amount of work done during the last ten years on the effect of modification of this substance. The section on the action of the opium group on the gastrointestinal tract is apparently taken verbatim from the 1928 text, and no references are made to the extensive recent work in this field. The amount of discussion of different groups of drugs does not always seem well balanced. For example, barbiturates are given five pages and the sulfone group of hypnotics half as many. Benzene and other cyclic hydrocarbons are discussed between the introductory section on the nervous system and that on alcohol. Both the U. S. P. and the B. P. preparations are listed without critical evaluation, but indication is not given as to the particular revision of either the Pharmacopeia of the United States or the British Pharmacopaeia intended.

It seems to the reviewer that a large manual of this sort, one that is probably too large for a textbook, ought to be as free as is humanly possible from errors of fact or implication, and its organization should be such as to make possible its use for reference with a minimum amount of effort. It is not enough that there be evidence of much labor. There is such evidence here, and there is here compiled a great deal of valuable material not always easy of access. But the apparent lack of a broad plan of organization and of an exacting editorial supervision has to a large degree nullified the efforts of the author. The book cannot be commended.

Treatment of Diabetes Mellitus. By Elliott P. Joslin, M.D., Sc.D.; Howard F. Root, M.D.; Priscilla White, M.D., and Alexander Marble, M.D. Price, $7.50. Pp. 783. Philadelphia: Lea & Febiger, 1940.

It is remarkable that so much new material can be incorporated in a revision of a book on a subject, diabetes, on which in the minds of many people information has been more or less static since the developments following the discovery of insulin. Joslin's standard book on diabetes in its present seventh edition has 756 pages of text, as compared with the sixth edition with 686 pages, which was published in 1937. There are new statistics, new facts and even new cooperating authors. The different chapters are revised and rewritten not only by the three, Root, White and Marble, who cooperated with Joslin in the sixth edition, but by others who appear as co-authors of chapters, including McDaniel, Pincus and Baldwin. Outstanding in the new material is the recognition by Joslin of the work of Best and Lukens on the relation of the anterior lobe of the pituitary gland to diabetes and to the pancreas itself. In his preface, Dr. Joslin says that it gives him a thrill to read that "diabetes resulting from the injection of anterior pituitary extract actually can be prevented," and to be told and shown that it can be cured, if as yet only in a dog or a cat. If prevention and cure are possible in an animal, why not in man?

The authors advocate treating the patient with diabetes so that the blood sugar is maintained at approximately normal figures while the patient is kept aglycosuric. This method is in contradistinction to that of some workers on diabetes who maintain that maintenance and physical well-being constitute the ultimate criterion for proper treatment of the diabetic patient.

It would be redundant to recount the contents of a book which has gone through seven editions, which is looked on as the bible of all who treat diabetic patients and which has had fulsome praise from every reviewer of previous editions. Suffice it to say that "Treatment of Diabetes Mellitus" by Joslin is a medical classic.

Rheumatic Fever. By May G. Wilson, M.D. Price, $4.50. Pp. 595. New York: The Commonwealth Fund, 1940.

This book, a summary of the author's experience in the observation of rheumatic fever in the first three decades of life, is based on first hand information obtained from the study of 647 subjects selected from 1,000 patients.

The first chapter contains a short but interesting historical summary of rheumatic fever. In the second chapter the epidemiologic aspects of the disease are dealt with and effects of climate, season, economic status, contagion and heredity are considered. The author concurs in the opinion of the English commission that overcrowding and poverty are not prime factors in the determination of the incidence of rheumatic fever and states that there is no conclusive evidence of contagion in the production of the disease, "although many of the facts are consistent with this view." The most arresting observation relating to the epidemiologic aspects is that heredity plays an extremely significant role in the production of rheumatic fever. For example, it was found that if both parents have a history of rheumatic fever, it may be predicted that the disease will affect practically all the progeny. If one parent has such a history and if one grandparent on the opposite side has a history of the disease, 50 per cent of the progeny will have rheumatic

fever. If this point of view is confirmed by other careful studies it will be of tremendous importance in any program in which reduction of the incidence of the disease is sought.

The fourth chapter concerns etiologic factors. Evidence for and against theories for the bacterial, allergic and virus origin of the disease is considered, and the conclusion is reached that there are serious objections to acceptance of any of the aforementioned factors as the proved cause of rheumatic fever. In this connection the author records her failure to produce rheumatic fever in chimpanzees inoculated with material obtained from patients with rheumatic fever. She refers to her experience that the incidence of positive blood cultures and the type of organism recovered were about the same among subjects recovering from acute infections as among patients suffering from rheumatic fever, and she concludes that infection of the respiratory tract is not a specific provocative agent in the occurrence of rheumatic fever.

Valuable chapters on pathologic changes, prognosis, criteria of diagnosis, significance of physical signs, roentgenographic and electrocardiographic studies and general and "specific" therapeutic measures follow. The inclusion of extensive and detailed records of the patients observed permits study of the material at first hand.

This record of a prodigious amount of personal observation and critical evaluation of a wealth of material should become required reading for the student of rheumatic fever.

Electrocardiography. By Chauncey C. Maher and Paul H. Wosika. Third edition, revised. Price, $4. Pp. 334, with 147 illustrations. Baltimore: The Williams & Wilkins Company, 1940.

The third, revised edition of Maher's book is a distinct improvement over the preceding ones. The detailed criticism of the second edition (*J. A. M. A.* **109**: 1223 [Oct. 9] 1937) has borne fruit in a thorough correction of some errors in the text, particularly in the presentation of the electrocardiograms. In the present edition, the electrocardiograms and their descriptions are on facing pages, an arrangement which simplifies the study of them and eliminates the interruptions in the text. An excellent correlation is achieved by presenting at the start of the book the classification of the Criteria Committee of the New York Heart Association and by rigidly adhering to its nomenclature throughout. The arrhythmias are well presented, as they should be. The chapter "The Electrocardiogram in Coronary Disease" is well done and should give the general reader a modern conception of this controversial subject. The electrocardiograms that illustrate this section are less striking than they might have been. In the cases of coronary occlusion, where serial electrocardiograms are reproduced, the time interval between tracings is excessively long, viz.: one, seven and seventy days; six hours and twenty-five days; twenty-four hours, two days and ninety days; one and four days. Furthermore, while the author points out that a later tracing is often necessary to corroborate a diagnosis of coronary occlusion, he does not make it quite clear that these later tracings follow a pattern of repair of the injury. The greatest usefulness of such tracings, then, is the evidence they supply of a normal (or uncomplicated) recovery from the accident. Chapter XIII, "Clinical Syndromes and Electrocardiographic Diagnosis," will appeal to the general reader who expects the electrocardiogram to clarify his clinical suspicions. The broad generalities in this section are probably correct, and the emphasis is properly placed on the electrocardiogram as but one of the diagnostic tools, rather than as *the* diagnostic tool, for cardiac disease.

The book would be considerably improved by three changes: 1. The use, as again suggested, of reproductions of the electrocardiograms rather than of retracings, which are often difficult to read. 2. A separate index of the electrocardiograms that illustrate the text, so that the busy student or practitioner can find sample tracings readily. The text would be easier to follow if when an electrocardiogram is referred to, the page on which it is reproduced is mentioned. 3.

More careful editing by the publishers. However, the book will be valuable to the students and the general practitioners who are seeking practical knowledge of electrocardiography presented in a manner that can be understood.

Strange Malady: The Story of Allergy. By Warren T. Vaughn, M.D., with a foreword by Esmond R. Long, M.D. Price, $3. Pp. 268. New York: Doubleday, Doran & Company, Inc., 1941.

Sponsored by the American Association for the Advancement of Science, this new book is the second of a series of nontechnical volumes on scientific subjects.

Allergy is a popular medical subject, and in this volume the general reader is told the story of allergy in a clear, readable style by an outstanding authority.

Many physicians will also appreciate and enjoy this review, and for senior medical students, interns or those intending to embark on the practice of allergy, the book will be an excellent introduction to the general subject.

The first portion of the book, devoted to the history and background of present day allergy, is particularly fascinating. Several of the men who contributed most to the subject of the relationship of immunology and allergy, such as Ehrlich, Sewall, von Behring and Calmette, were contemporaries and friends of the author's father, Dr. Victor Vaughn, himself a pioneer in the field. Hence the author is able to draw on memories and anecdotes of these great men, thereby adding much to the interest and value of this portion of the book. Ehrlich's side chain theory of the processes of immunity and allergy is clearly presented, but to make the material entirely unmistakable excellent line drawings and cartoons illustrating the theory accompany the text.

The second portion describes allergic diseases, their numerous causes, how the causative agent is found and how allergic diseases are treated. The layman will enjoy this portion as he would a series of short detective stories.

The internist or neurologist will probably not agree with the statement that migraine headache is one of the "commoner allergic diseases." The consulting allergist, however, doubtless sees a higher incidence of allergic headache than does the physician in general practice. The internist also may question the opinion that "sensitization to foods is the commonest form of human allergy" and may not have the confidence in cutaneous tests with food antigens that may be inferred from the chapter on "Forbidden Fruit."

The closing chapters deal somewhat with problems for the future and the part that nervous factors, internal secretions, histamine and so forth may play in the development of allergic conditions.

Bacteriology in Neuropsychiatry. By Nicholas Kopeloff, Ph.D. Price, $4.50. Pp. 316. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

This is a readable survey of an enormous amount of literature on the infectious diseases which may be related to pathologic conditions of the human nervous system. The book is particularly valuable as an aid to the investigator. Although it is by no means a complete textbook on bacteriology, it has covered many fields not dealt with in texts, particularly the investigation on the bacteriology of the so-called functional nervous diseases. There are eight chapters on the possible relationship of infection to the functional psychosis and to epilepsy. Combing the literature and offering the results of his own work in this field, the author discounts focal infection, autointoxication and "filterable forms of tuberculosis" as being of primary importance in such conditions; also, he finds that the body fluids of psychotic patients do not differ substantially from those of normal persons. There are four interesting chapters on allergy and hypersensitiveness.

The following items were of interest: The epidemiologic studies on the encephalitis occurring in St. Louis suggest the possibility of rodents being a vector in the spread of the disease. Anterior poliomyelitis virus is present in the gastrointestinal tract of patients, and there is considerable evidence for the spread of the virus via sewage. In regard to smallpox, it is interesting that the number of

cases of postvaccinal encephalitis is declining. Mumps may spread through army camps, and the disease shows a high incidence of associated mild meningoencephalitis. Influenza virus exists as a saprophyte in the larva of the swine lung worm, as has been shown by Francis. Attention is called to Stanley's statement that the basic unit of the filtrable virus is a "gene, perhaps a single nucleoprotein molecule."

Possibly the greatest value of the book is the clarifying of the significance both of a large amount of confusing literature and of a number of bacteriologic studies of questionable worth.

Management of the Cardiac Patient. By W. G. Leaman Jr., M.D., Assistant Professor of Medicine, Woman's Medical College of Pennsylvania. Price, $6.50. Pp. XX + 705, with 255 illustrations. Philadelphia: J. B. Lippincott Company, 1940.

Heart disease, no doubt, deserves unending attention. This new textbook is a workman-like affair, clearly printed, delightfully illustrated, well indexed and not too heavy for comfortable use in spite of its length. When the second edition appears, a better picture of William Withering or an improved reproduction of the title page of the first edition of his "Account of the Foxglove" would make a more dignified frontispiece than the one now used. This, however, is a minor criticism.

The book is built along orthodox lines and reads easily. Certain subjects which often receive scant attention in medical texts are properly emphasized: social service, physical therapy, occupational therapy and prescribed exercise. The surgical and obstetric aspects of heart disease also receive the serious consideration which they deserve.

The book is pleasant to meet.

An Introduction to Biochemistry. By W. R. Fearon. Second edition. Price, $3.75. Pp. 475. St. Louis: C. V. Mosby Company, 1940.

This is a textbook of 475 pages. The approach to the subject is with special emphasis on inorganic biochemistry, with correspondingly less emphasis on organic chemistry, tissue chemistry, blood, muscle and nerve.

This, the second, edition has been largely rewritten. Special chapters are provided for solutions and colloidal systems, steroids, pigments, tissue respiration and internal environment.

References are placed at the end of each chapter.

The difference in emphasis notable among British writers on biochemistry is exemplified in that as much space is devoted to the effect of onium salts on the maintenance of fluid equilibrium in elasmobranchs as is given to the essential amino acids (one-third page).

The material is presented in brief, concise form and is adequately systematized.

Synopsis of Materia Medica, Toxicology and Pharmacology. By Forrest Ramon Davison. Price $5. Pp. 633, with 45 illustrations. St. Louis: The C. V. Mosby Co., 1940.

Here indeed is an excellent book of convenient size including the essentials of materia medica, toxicology and pharmacology. Introductory chapters deal with such subjects as basic principles of pharmacology, prescription writing and toxicology, and these are followed by systematic discussions of various groups of drugs. Of special value to the physician are the pages dealing with newer drugs, in regard to which material is hard to find in most textbooks. Diagrams, kymographic tracings and drug formulas enrich the text, which is well printed on substantial paper.